Studies in the synthesis of dopamine agonists

Cosford, Nicholas D. P.

Award date:
1989

Awarding institution:
University of Bath

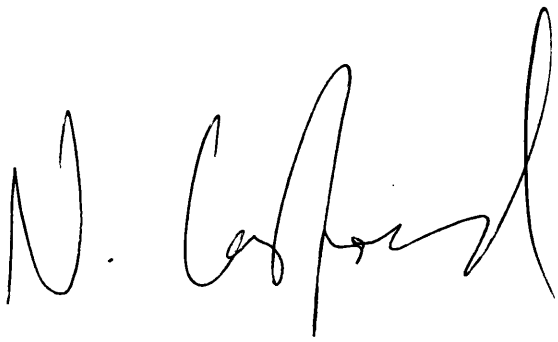
STUDIES IN THE SYNTHESIS OF DOPAMINE AGONISTS

submitted by NICHOLAS D. P. COSFORD

for the degree of Doctor of Philosophy

of the University of Bath

1989.



ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

"Three passions, simple but overwhelmingly strong, have governed my life: the longing for love, the search for knowledge, and unbearable pity for the suffering of mankind."

(From the Autobiography of Bertrand Russell, Prologue).

To my Father.

Acknowledgements.

I would like to thank all the people who have made this work possible. My supervisors, Professor Malcolm Campbell and Dr. Malcolm Sainsbury, and my industrial supervisor, Dr. Duncan Rae, for their tireless enthusiasm and encouragement, and for the many helpful discussions. I acknowledge and thank the SERC and Organon SDG for funding the CASE award.

I would like to thank all the staff and students in the School of Chemistry, and the workers at Organon SDG, for making the three years enjoyable. Thanks to Sue Boucher, John Bradley, Dave Wood, Harry Hartell, Chris Cryer, Alan Carver, Andy Osprey and Roy Lapper for their excellent technical support, and Paul Graupner, for help with high field n.m.r. experiments. I would also like to thank all the secretaries, too numerous to mention by name, in the Organic department over the three years, for their invaluable help.

I am indebted to the members of the Molecular Graphics Unit for their assistance in the compilation of this thesis, and to Phil Evans, Paul Graupner, Malcolm Sainsbury, Russell Viner and Nick Huby for reading proofs. Thanks and love to Deborah for putting up with me!

Finally, I would like to thank my parents, for their love and support.

(The work presented in this thesis was carried out between October 1985 and September 1988).

Contents

Abstract.

Synthetic routes to the preparation of 1-(2-pyridyl)-3-buten-2-one (53) and *1-(2-pyridyl)-3-butyn-2-one* (54) have been studied. Whilst it was found that these compounds could not be prepared using our methods, several new 2-pyridylalkanol derivatives were synthesised using the reactive species 2-picolyl-lithium. This methodology allowed access to *1-(2-pyridyl)-1-buten-3-yne* (48) and 1-(2-pyridyl)buta-1,3-diene (50) and these were reacted with nitrile oxides to give a number of new isoxazoles and isoxazolines. *Ethyl 5-[2-(2-pyridyl)ethenyl]isoxazole-3-carboxylate* (45) was converted to the 3-amino derivative using a Curtius rearrangement.

It was found that these pyridoisoxazole stilbene analogues did not undergo oxidative photochemical cyclisation to the corresponding tricycles. A similar result was obtained for *4-[2-(2-pyridyl)ethenyl]-2-thiazolamine* (41), which was prepared from the novel chloromethylenone (113). Thus, access to a range of novel heterocylic stilbene analogues has been demonstrated.

An extensive study of the reduction of the pyridyl portion and the unsaturation in the ethenylthiazolamine (41) was undertaken. The pyridines were reduced by quaternization with alkyl halide followed by treatment with sodium borohydride. Although hydrogenation was complicated by the sulphur atom in the thiazole moiety, di-imide and sodium hydrotelluride were found to be effective for this purpose. As a result of this work several new 2-substituted tetrahydropyridines have been prepared and their structures elucidated using various high field n.m.r. techniques. It has been shown that the size and type of the *N*- and 2-pyridyl substituents determines the position of the double bond in the tetrahydropyridyl ring following sodium borohydride reduction.

A novel palladium mediated alkene-aryl coupling reaction between styrene

(154) and 2-thiazolacetamide (158) has been demonstrated, and this may find use in future synthetic work.

Abbreviations.

Ac	Acetyl.
Ar	Aryl.
AMP	Adenosine monophosphate.
ATP	Adenosine triphosphate.
t-Bu	Tertiary butyl.
CI	Chemical ionisation.
CNS	Central nervous system.
COSY	Correlation spectroscopy.
m-CPBA	*m*-Chloroperbenzoic acid.
CRM	Circling Rat Model.
DA	Dopamine.
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene.
DCC	1,3-Dicyclohexylcarbodi-imide.
δ_H	Proton chemical shift in parts per million.
δ_C	Carbon chemical shift in parts per million.
DMF	*N*,*N*-Dimethylformamide.
DMSO	Dimethyl sulphoxide.
DNP	2,4-Dinitrophenylhydrazine.
DOPA	3,4-Dihydroxyphenylalanine.
EI	Electron impact.
Et	Ethyl.
eV	Electron volt.
EPS	Extrapyramidal side effects.
Fig.	Figure.
g.l.c.	Gas-liquid chromatography.

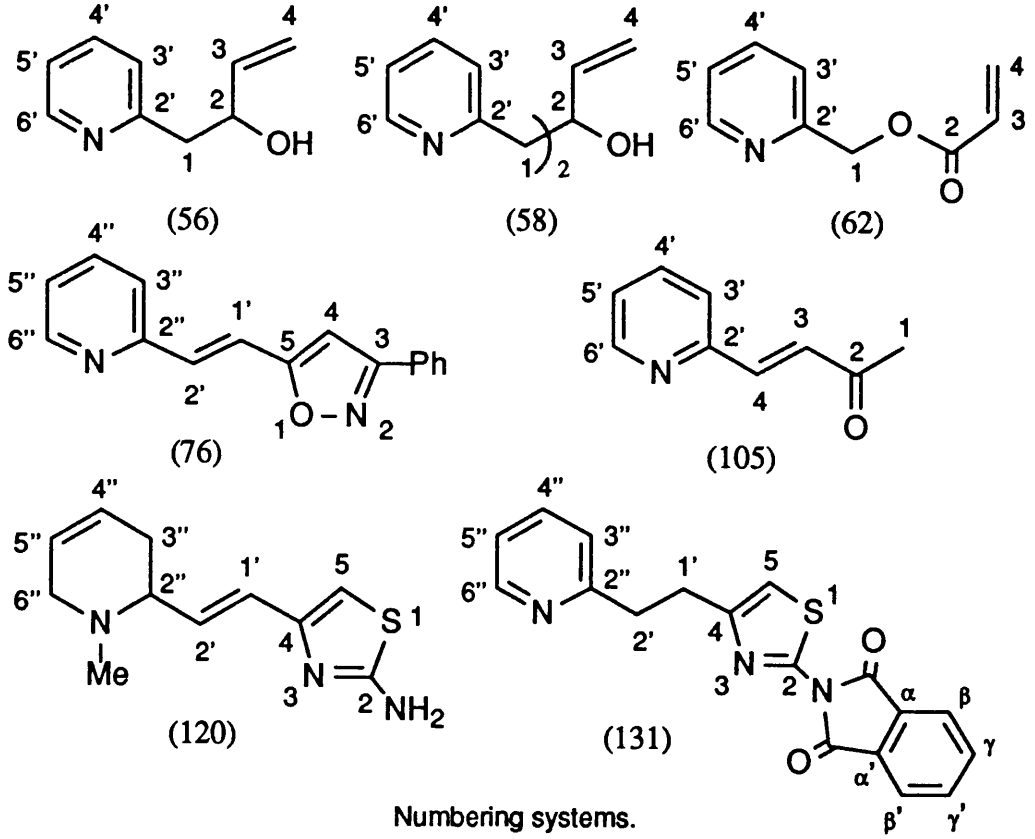
GTP	Guanosine triphosphate.
h	Hour.
Het.	5-Membered heterocycle.
^{3}H-NPA	*N*-Propyl apomorphine Binding Assay.
5-HT	5-Hydroxytryptamine.
i.r.	Infra red.
lit.	Literature.
J	Coupling constant.
LMAM	Mouse Ambulation.
LDA	Lithium di-isopropylamide.
LSD	Lysergic acid diethylamide.
Me	Methyl.
MEK	2-Butanone (methyl ethyl ketone).
m.p.	Melting point.
m/z	Mass:charge ratio.
m.s.	Mass spectrometry.
n.m.r.	Nuclear magnetic resonance.
PCC	Pyridinium chlorochromate.
PDC	Pyridinium dichromate.
Ph	Phenyl group.
Pr	Propyl.
Py	2-Pyridyl group.
R	Alkyl.
R_F	Retention factor.
REA	Rabbit Ear Artery.
SAR	Structure/activity relationship.
Solv.	T.l.c. elution solvent system.

TD	Tardive dyskinesia.
THF	Tetrahydrofuran.
t.l.c.	Thin layer chromatography.
TMEDA	*N,N,N',N'*-Tetramethylethylenediamine.
TMS	Tetramethylsilane.
u.v.	Ultra violet.

Nomenclature and Numbering of Compounds.

All new compounds discussed in the text have been named according to the IUPAC conventions. In the case of 3-aminoisoxazole and 2-aminothiazole derivatives a slight modification has been made in order to simplify the full names. In accordance with the system used by *Chemical Abstracts* they have been renamed as derivatives of 3-isoxazolamine and 2-thiazolamine. Thus, the tetrahydropyridine (120) becomes *4-[2-(N-methyl-1,2,3,6-tetrahydropyrid-2-yl)ethenyl]-2-thiazolamine.* In other instances, names have been used as quoted in the literature.

The numbering systems employed when discussing spectra are illustrated by the examples in the diagram below. In most cases the numbering follows the IUPAC name, with the exception of (58), (62) and (65). Greek characters have been used when referring to the phthalimide ring positions in the phthalimido derivatives of the 2-thiazolamines *e.g.* (131). A full list of diagrams of the major compounds mentioned in the discussion and experimental sections appears in the appendices.

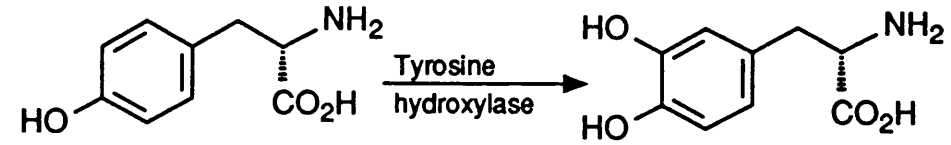


Numbering systems.

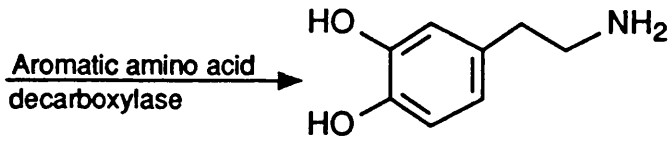
INTRODUCTION.

1.1 The Neurochemistry of Dopamine.

The transmitter substance dopamine (DA, 3) is found in the human peripheral nervous system as well as the central nervous system (CNS). Like the other catecholamines, adrenalin and noradrenalin, it is biosynthesised in neurons from the amino acid tyrosine, (scheme 1.1).[1]



(1) (2)



(3)

Scheme 1.1.

The biosynthetic precursor tyrosine (1) is absorbed from the bloodstream. In the neurons, it is converted to L-DOPA (2) by the enzyme tyrosine hydroxylase, and decarboxylation to DA is accomplished by the action of aromatic amino acid decarboxylase.

In the central nervous system, dopamine has been identified as the neurotransmitter in several neuronal networks sited specifically within the brain itself.[2,3] The major dopaminergic tracts appear to be important in the coordination of muscle movement (the nigrostriatal system) and complex thought processes (the mesolimbic and mesocortical systems). One other central dopaminergic system, the tuberoinfundibular, is involved with the regulation of the enzyme prolactin, which is essential

for milk production as well as other important processes. This neuronal system is often used in biological testing to indicate that compounds are dopaminergically active.

The nigrostriatal system consists of cell bodies located in the substantia nigra, with axons that project into the striatum within the basal ganglia. Hence this neuronal pathway appears to be involved with motor function. Another of the mid brain stuctures, the tegmentum, is linked firstly to the limbic forebrain by the mesolimbic system, and secondly to the limbic cortex by the mesocortical system. Since these neurons extend into the cortex of the brain, it is believed that they are essential for the control of emotional behaviour, as well as other thought processes, including memory.

The identification and classification of dopamine receptors has been an area of extensive research (table 1.1).[4,5] Early receptor binding studies had indicated the existence of four distinct receptor subtypes; D-1, D-2, D-3, and D-4. Evidence now shows that both the D-1 and D-2 receptors possess a high and low affinity state. The high affinity state of each may be converted to the low affinity state in the presence of guanosine triphosphate, (GTP). Hence, the low affinity D-2 binding site corresponds to the D-2 receptor, whilst the D-4 receptor is now believed to be the high affinity D-2 site. This high affinity site has been identified as the D-2 autoreceptor (presynaptic receptor) in the CNS. Similarly, the low affinity D-1 site is the D-1 receptor and the high affinity site is the D-3 receptor, which may correspond to the D-1 autoreceptor but this is unconfirmed.

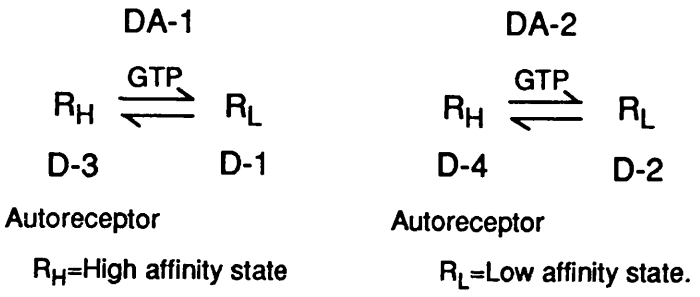


Fig. 1.1.

Classification of Dopamine Receptors.				
	D-1	D-2	D-3	D-4
Adenylate cyclase association.	Stimulates.	Inhibits or unassociated.	Inhibits or unassociated.	?
Typical location.	Striatum.	Striatum, hypophysis.	Nigrostriatal terminals.	Corticostriatal terminals.
GTP sensitivity.	Low affinity for antagonist.	Low affinity.	High affinity.	High affinity.

Table 1.1.

The D-1 and D-2 receptors are biochemically and pharmacologically distinct. The D-1 receptor is linked to the stimulation of adenylate cyclase, which converts ATP to cyclic AMP. The receptor type D-2 however is linked to a regulatory protein that inhibits adenylate cyclase activity. It is the latter of the DA binding sites which constitute the majority in the CNS, with about 60% in the region of the substantia nigra and striatum.

In summary, (fig. 1.1), dopaminergic receptors DA-1 and DA-2 in the CNS each possess a high and low affinity state, the DA-2 high affinity state corresponding to cell body autoreceptors. The receptors are characterised by a positive (DA-1) or negative (DA-2) link to adenylate cyclase.

1.2 Dopamine and Parkinson's Disease.

Of the diseases which affect the central nervous system, Parkinson syndrome is probably the most well characterised.[2, 6] It is the third most common neurological disease, affecting 7% of people above age 65 and about 0.1% of the whole population.

It is an extremely debilitating disease in which motor function progressively degenerates. The symptoms are firstly, muscular rigidity causing a flexed or simian (apelike) posture. Secondly, there is an overall immobility of the facial muscles accompanied by speech problems and difficulty in swallowing. Thirdly, the sufferer will have a shuffling gait and find it difficult to initiate movement (akinesia), and this means that there is a tendency to run rather than walk. Finally, the patients possess an exaggerated, rhythmical muscle tremor in the limbs of 3–5 Hz.

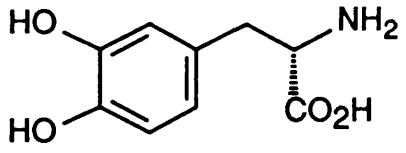
The Parkinsonian symptoms are caused by damage to dopaminergic neurons within the CNS. This dysfunction may be due to degeneration with age, or diseases, such as syphilis, may be responsible. Also, reserpine and many of the narcotic drugs are known to cause Parkinson like symptoms.

The damaged neurons, which almost certainly form part of the nigrostriatal system, perform an inhibitory function in the basal ganglia that normally suppresses the muscle tremor and rigidity. This neuronal malfunction leads to a decrease in the amount of dopaminergic transmission within the system and hence the symptoms arise.

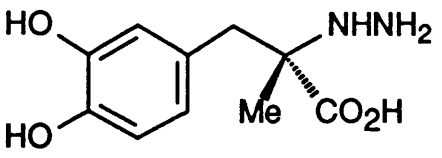
The treatment for Parkinsonism has been based around improving the dopaminergic flow in the CNS. This is accomplished to a certain extent by administering L-DOPA (2), the biosynthetic precursor of dopamine. The L-DOPA is presumably taken up by the remaining healthy neurons which then convert it to DA (3) in order to compensate for the damaged cells. An alternative theory is that other cells containing DOPA decarboxylase, such as serotonergic neurons, use the administered L-DOPA to create enough DA to innervate the nigrostriatal target cells.

There are however drawbacks in the use of L-DOPA therapy. Because it is rapidly metabolised in peripheral organs, extremely large oral doses are required – about 4–5g per day. Of this amount, less than 0.1% reaches the brain. These excessive doses have unpleasant side effects, such as athetosis, a slow, writhing

involuntary movement of the hands and neck, as well as nausea and vomiting. Efforts to reduce the quantities of L-DOPA required have included the use of carbidopa (4, fig. 1.2), a hydrazine analogue of α-methyl DOPA. Carbidopa has a greater affinity for DOPA decarboxylase than L-DOPA and is preferentially metabolised within the peripheral nervous system. Hence about 80% less L-DOPA is required to treat the symptoms when administered with carbidopa.



(2)



(4)

Fig. 1.2.

L-DOPA therapy is far from being a cure for Parkinsonism: it merely controls some of the symptoms for a few years, after which time its effects tend to wear off and the patient reverts to the former rigid, tremulous state. Thus there is a definite need for a cure, or at least a much improved treatment for the disease.

1.3 Dopamine and Schizophrenia.

Schizophrenia is the most serious of the mental illnesses. [2] It is the major cause of psychiatric hospitalisation: victims of the disease occupy about 20% of all hospital beds in the U.S.A., and before the advent of psychotherapeutic drugs in the 1950's it accounted for half of all hospital bed occupancy. It primarily strikes teenagers and young adults.

The term schizophrenia means literally a "splitting of the mind" and was first used by the Swiss scientist Eugen Bleuler at the end of the last century. It describes

the main characteristic of the disease, that is the separation of the cognitive (learning) processes from the emotional side of the personality. It is therefore different from the very rare condition known as "split personality", where the sufferer possesses two separate identities.

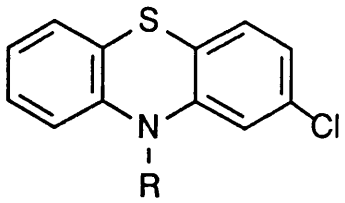
The symptoms of the disease follow an alternating pattern of two distinct phases: episodes of psychosis lasting a few weeks are separated by much longer periods when the patient exhibits residual symptoms. The psychotic episodes, termed positive symptom schizophrenia, are characterised by bizarre delusions, for example of being controlled by an outside force or of persecution, as well as auditory hallucinations, *i.e.* hearing voices commenting on one's actions. The residual phase, or negative symptom schizophrenia, is indicated by a disorder of thought processes, consisting of incoherence, the loss of normal association of ideas, poverty of speech, and a lack of emotional responsiveness (flattening of affect).

Until the 1950's, no treatment was specifically effective for schizophrenia. Then in 1953 a treatment was discovered which had as great an impact on the field of mental health as the discovery of penicillin had on the treatment of infective disease. Chemists at Rhone Poulenc synthesised chlorpromazine (5) whilst searching for a compound with improved antihistaminic properties. Henri Laborit, a surgeon at the Hospital Boucicaut in Paris found that the drug sedated patients suffering from post operative shock. As a result of this work, the psychiatrist Pierre Deniker tested the compound on some of his chronically mentally ill patients. He immediately recognised the major calming effect of the drug on patients with positive symptom schizophrenia.

Within hours of treatment the drug exhibited a sedative effect by calming acutely agitated patients, but more importantly, over several weeks the delusions and hallucinations were abolished, and the thought processes returned to a more normal state. Drugs showing this long term effect are known as antipsychotics, or neu-

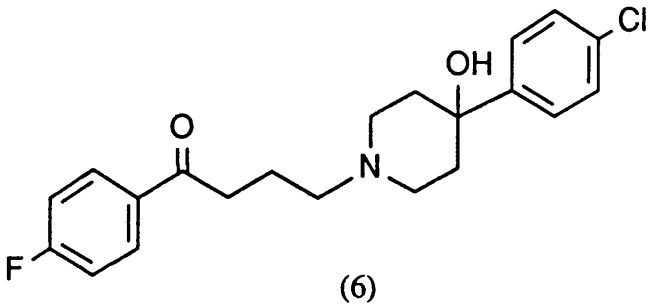
roleptics.

The discovery of chlorpromazine (Largactil) as the first antipsychotic led to the synthesis of a whole range of compounds bearing the phenothiazine nucleus, as well as many other compounds exhibiting activity as antipsychotic agents. These include the butyrophenones, *e.g.* haloperidol (6), and the diphenylbutylpiperidines, *e.g.* pimozide (7), fig. 1.3.

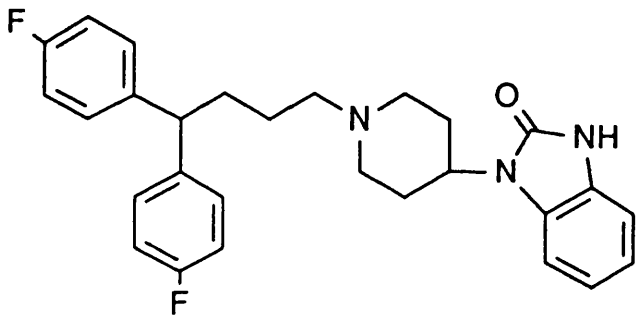


(5)

R=$(CH_2)_3NMe_2$



(6)

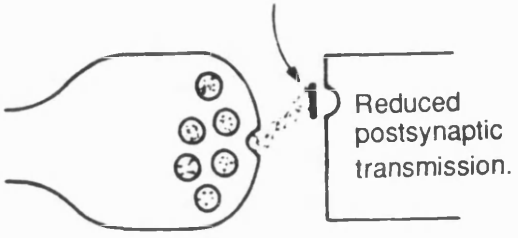


(7)

Fig. 1.3.

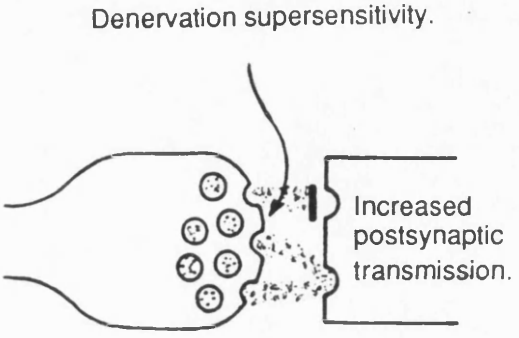
It was originally believed that these drugs were merely tranquilisers. By the mid 1960's however it had been shown that all antipsychotics shared the property of blocking dopamine receptors in the CNS. More specifically, it was found that drugs that are effective neuroleptics in man are DA-2 antagonists.[4] In addition, many neuroleptics are DA-1 antagonists, but this does not appear to be essential for antipsychotic activity.

These conclusions were due in part to an analysis of the major side effects of the drugs. It was noticed that patients treated with neuroleptics in the short term (*i.e.* after acute administration) often developed symptoms resembling Parkinsonism. These included hand tremor and muscular rigidity, and were termed extrapyramidal side effects (EPS). An explanation for these observations would be that the antipsychotics blocked DA receptors in the nigrostriatal pathway, reducing the flow of dopamine in that system in the short term, with the Parkinson-like EPS being the result, (fig. 1.4a).[2,3]



Antipsychotic effects (mesolimbic).
Extrapyramidal reactions (nigrostriatal).

Fig. 1.4a.



Initial disappearance of Parkinson's syndrome.
Onset of tardive dyskinesia.

Fig. 1.4b.

Chronic administration of antipsychotic drugs in up to 10% of cases results in the condition known as tardive dyskinesia (TD). This manifests itself in the form of abnormal oral, facial and tongue movements, chorea (rapid, flick-like movements of the limbs and facial muscles) and athetosis. These side effects are usually temporary, and may be eradicated by ceasing administration of the offending drug, but the symptoms are in some cases permanent.

Interestingly, the clinical pharmacology of the syndrome is very different from Parkinsonism, but is more similar to diseases caused by an excess of DA function. This somewhat surprising observation may be explained if prolonged neuroleptic drug treatment leads to almost total DA receptor blockade, causing the condition in

the neurons known as supersensitivity. These neurons have a greatly increased number of receptor sites and an abnormally high rate of synthesis and release of their transmitter substance. The combination of overproduction and more receptors together results in a much greater conductivity of the neurons, hence the term "supersensitive". Thus the excess DA released into the nigrostriatal system has the nett effect of causing tardive dyskinesia (fig. 1.4b).

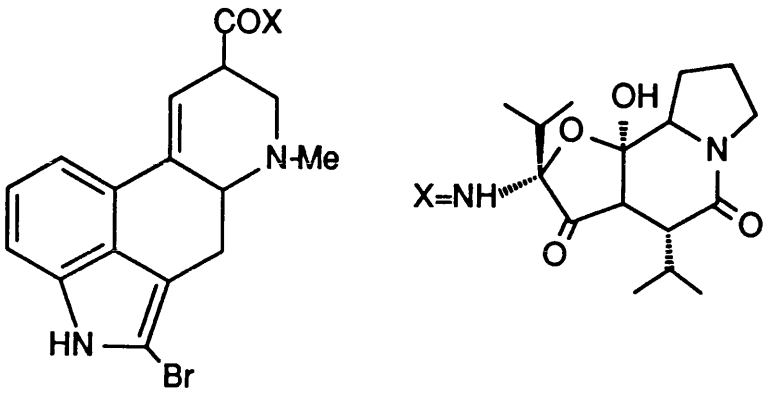
These observations, combined with other biochemical studies, have resulted in a Dopamine Hypothesis of Schizophrenia.[2,3] In its simplest form this states that schizophrenia may be related to a relative excess of central dopaminergic neuronal activity. The most likely centres for this increased activity are the mesolimbic and mesocortical systems. It must be stated however that although there is a great deal of data to support the hypothesis, there is as yet no direct experimental evidence.

During the course of other studies it has also been observed that certain drugs, such as cocaine and the amphetamines, can induce psychotic syndromes resembling paranoid schizophrenia, and that antipsychotic drugs act as an antidote. This is explained by the fact that cocaine, like the ergot alkaloids and many other compounds, shows dopamine agonistic behaviour. Hence DA antagonists such as chlorpromazine (5) are likely to counteract their effect.

1.4 Dopaminergic Agents in the CNS.

It has already been pointed out that Parkinson's disease is due to a lack of dopaminergic function. Therefore, the administration to patients of an efficient post-synaptic DA agonist with few side effects would represent either a cure or a greatly improved therapy. An advance made in the early 1970's was the introduction of the drug bromocryptine (8, fig. 1.5), an ergoline derivative.[6-9] It is a specific DA-2 agonist at low doses and has been used as an antiparkinson agent, particularly in patients who have become immune to L-DOPA treatment. Although the compound has a

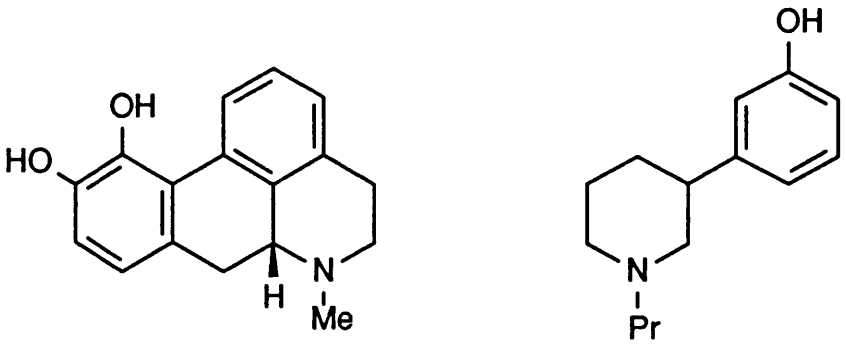
proven efficacy, it exhibits some psychiatric side effects which preclude its use on a larger scale.



(8)

Fig 1.5.

Another extremely important property of certain DA agonists is demonstrated by the prototype drug apomorphine (9, fig. 1.6). [10-12] It was discovered that this compound not only acts postsynaptically, but also activates presynaptic receptors. In fact, in some systems apomorphine is ten to twenty times more potent in stimulating DA autoreceptors than the corresponding postsynaptic receptors.



(9) (10)

Fig. 1.6.

The potential of DA autoreceptor agonists lies in their ability to reduce the output of dopamine from neurons by inducing a response presynaptically and hence regulating DA synthesis and release. A reduction in the rate of DA output by the innervation of autoreceptors overcomes the need for receptor blockade and consequent EPS and TD syndromes. Hence, this type of drug action could theoretically replace the antipsychotics as the main treatment for schizophrenia, and in particular may prove to be an effective therapy for the negative symptoms.

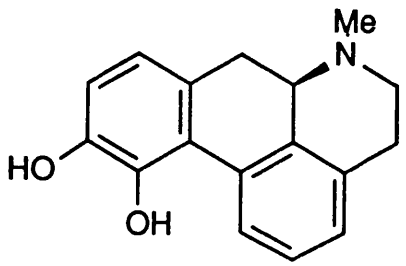
The clinical use of apomorphine is limited by poor oral absorption, short duration of action, and like some other DA agonists, by its action at the vomiting centre of the brain stem, causing its emetic properties. However, the compound has been vital as a model in many structure/activity relationship (SAR) and biological data studies.

One such study yielded the interesting dopamine mimic 3-(3-hydroxyphenyl)-*N*-propylpiperidine, or 3-PPP (10, fig. 1.6).[3, 10, 13] This compound is of particular interest in that testing performed on the racemate showed it to be a specific DA autoreceptor agonist, apparently exhibiting no postsynaptic activity. However, it was found that the resolved isomers differ significantly in their pharmacological profiles. Thus the (+)-3R enantiomer behaves like a classical DA receptor stimulant, agonising both autoreceptors (low doses) and postsynaptic receptors (high doses). By way of contrast the (-)-3S enantiomer activates autoreceptors at low doses, but unexpectedly blocks postsynaptic receptors at higher doses. The nett effect of racemate administration is therefore selective autoreceptor stimulation, with the action of the enantiomers postsynaptically in opposition (table 1.2). These findings have prompted investigations into the relationship between the absolute stereochemistry of other DA analogues and their site of action.

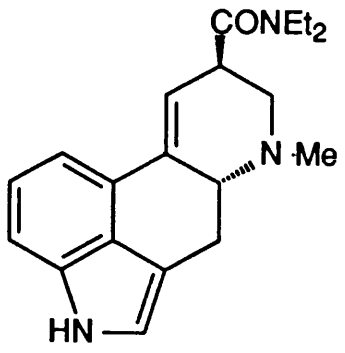
Biological Activity of 3-PPP.		
	Low Doses.	High Doses.
3R	Autoreceptor agonist.	Postsynaptic agonist.
3S	Autoreceptor agonist.	Postsynaptic antagonist.
Racemate.	Autoreceptor agonist.	

Table 1.2.

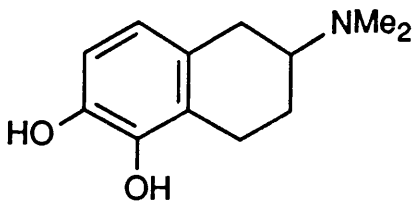
Amongst the most important SAR studies have been those which have focused on deducing the active portions of the apomorphine and ergoline molecules. It has now been well established by the work of Cannon and others [14–16] that the active moiety within apomorphine is the rigid dopamine–like structure, as in fig. 1.7.



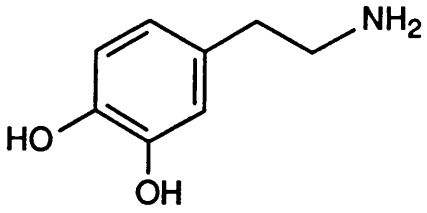
(9a)



(12a)



(11)



(3)

Fig. 1.7.

Apomorphine (9a, 9b) is of the R absolute configuration at carbon-6a and the corresponding S enantiomer is inactive as a DA agonist. In attempts to elucidate the active site, Cannon prepared the racemic 2-aminotetralin partial structure (11) and found it to be very comparable in activity to apomorphine itself. Other analyses have confirmed these findings.

On the other hand, when the structure of LSD (12a) is examined, it is not immediately obvious as to which portion of the molecule confers dopamine agonist properties. The question is compounded by the fact that the ergolines show many pharmacological properties other than DA agonism, such as 5-HT antagonism and hallucinogenic effects. Nevertheless, some groups have assumed that the rigid β-phenethylamine portion (12a, figs. 1.7, 1.8) is the moiety responsible for DA agonist properties. On closer inspection, however, this assumption is not supported, and has been challenged initially by Nichols,[17] and later by Kornfeld and coworkers.[18]

The natural ergolines have the R absolute configuration at 5-C as shown, (fig. 1.8), *i.e.* α to the amino function, and once again the S enantiomers are inactive. Thus it is obvious that the stereochemistry is critically important. If the structures (9a) and (12a) are examined, it may be noted that the hydrogen atoms at 6a-C and 5-C respectively in the corresponding fragments are of opposite configuration. Kornfeld thought it highly unlikely therefore that the phenethylamine portion of LSD (12a) corresponds to the rigid DA structure in apomorphine (9a). If this were the case, it would be the inactive, unnatural S-ergolines which correspond to the active R-apomorphine if the two β-aminotetralin moieties were compared.

However, if the two molecules are rewritten as in (9b) and (12b)(fig. 1.8), an alternative mode of comparison is evident. In this pair, it is now the rigid, pyrrole-ethylamine portion in (12b) which corresponds to the dopamine portion in (9b). The hydrogen atoms at 5-C and 6a-C respectively in this analogy are now of the same configuration. Thus it was suggested by Kornfeld that, as a working hypothesis, the

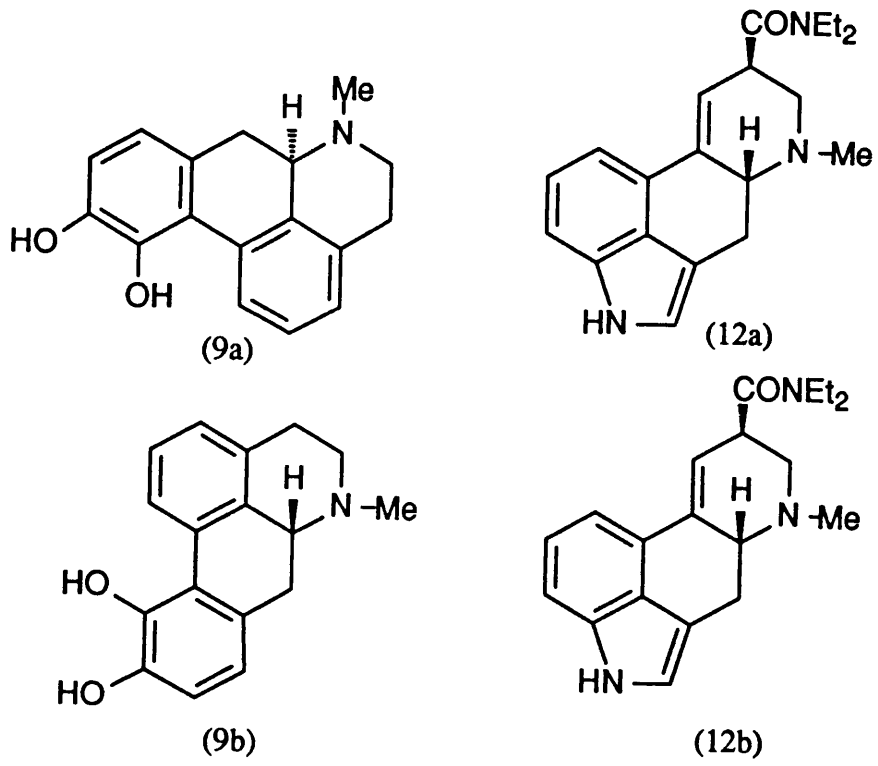


Fig. 1.8.

rigid pyrrole-ethylamine moiety in the ergoline class should be regarded as being responsible for DA agonist properties, rather than the phenethylamine. Subsequent analyses, which have generally involved the synthesis and testing of heterocyclic analogues have added weight to this theory.[19]

Research has also been carried out on 2-aminotetralins substituted in various ways, both in the aromatic nucleus and the 2-amino function.[20-22] Intriguing results have been presented by McDermed *et al.*, who studied resolved 2-aminotetralin derivatives. [23] The first compound to be resolved was 5-hydroxy-2-(dipropylamino)tetralin (13, fig. 1.9).

The S enantiomer [13(S)] was found to be about ten times more potent than apomorphine, whilst the R enantiomer [13(R)] was inactive at the doses tested. The work was continued with the resolution and pharmacological evaluation of (14), (15)

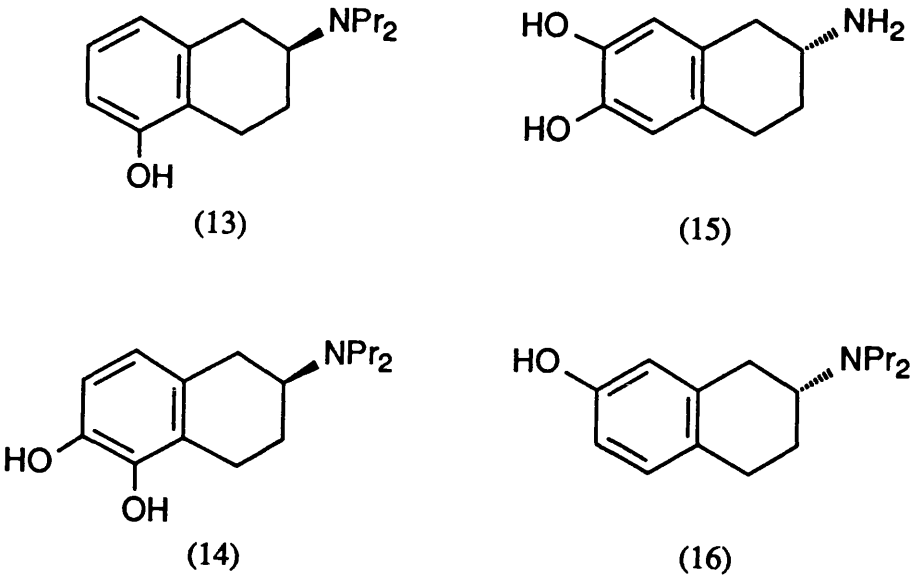
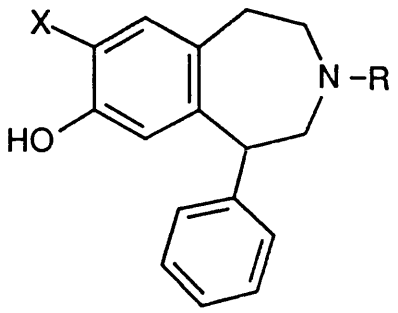


Fig. 1.9.

and (16). It was found that the stereochemistry at carbon 2 for the more active enantiomer was S in the case of compounds (13) and (14), whereas it was opposite for compounds (15) and (16). Interestingly, in a later study, 7-hydroxy-2-(*N*,*N*-dipropylamino)tetralin, [16(S)], proved to be the most selective presynaptic agonist of the derivatives tested.[22] These results were organised within the context of a hypothetical DA receptor model, of which there have been several other studies. [4, 24]

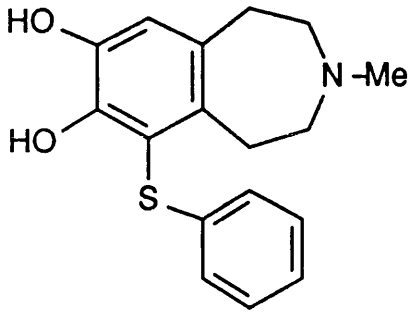
Although the area of presynaptic versus postsynaptic drug action has been extensively researched, it is far from being the sole criterion of study and evaluation. Efforts have also been directed towards the design of compounds which distinguish between receptor sub-types, *i.e.* showing DA-1 and DA-2 specificity. Earlier, there was some doubt as to whether the central DA-1 binding site could actually be called a receptor since no central effects were known to be mediated through it. Now, however, the DA-1 receptor has been shown to be involved with some behavioural responses. SCH-23390 (17a, fig. 1.10), the first selective DA-1 antagonist to be described is effective in blocking locomotor activity induced by amphetamine - a

reaction formerly believed to be mediated exclusively through the DA-2 receptor. [4, 25-28] The compound exhibits a >500-fold greater affinity for the DA-1 receptor over the DA-2 receptor, and is very potent at inhibiting dopamine stimulated adenylate cyclase.



(17)

17a. R=Me, X=Cl
17b. R=H, X=OH
17c. R=Me, X=OH
17d. R=H, X=Cl
17e. R=Me, X=Br



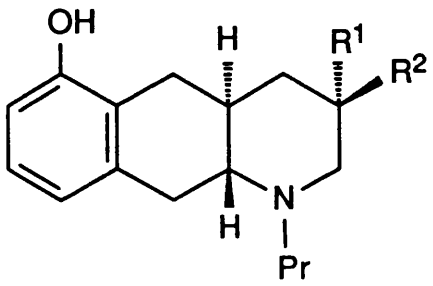
(18)

Fig. 1.10.

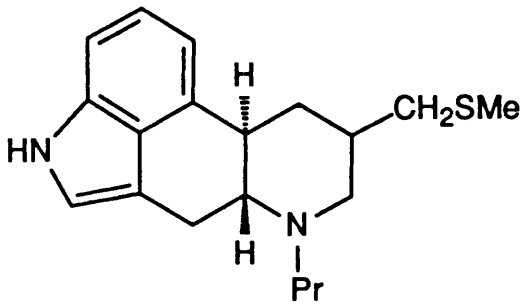
An analysis of some analogues of SCH-23390 has illuminated the structural requirements for DA-1 receptor activity. For example, SKF-38393 (17b) is a DA-1 agonist. [4, 25-29] *N*-Methyl substitution, as in SKF-7560 (17c), yields a partial agonist, whilst the 7-chloro derivative, SKF-83509 (17d), is a pure antagonist of moderate potency. SCH-23390 clearly incorporates both of these changes and is a much more potent antagonist. [30] The 7-bromo derivative, SKF-83566 (17e) is also a selective DA-1 antagonist, and like SCH-23390, this activity is stereo-specific with respect to the R enantiomers. [31] Finally, SKF-83742 (18), has also been reported to be a DA-1 antagonist. [4, 32]

Several new compounds have been synthesised which exhibit potent and, in some cases, selective DA-2 agonist activity. Sandoz workers have reported the

preparation and prolactin secretion inhibiting activity of CV-205-503 (19a) and CV-205-502 (19b, fig. 1.11).[33] These are benzo[*g*]octahydroquinolines in which the 3-C sidechain corresponds to the 8-C substituent of the ergolines. In fact, the methylthiomethyl group of 19a is conceptually derived from pergolide (20). This important ergoline derivative is a DA agonist which has controlled tremors induced in monkeys, and has proved to be effective in the treatment of Parkinson's disease. Whilst neither 19a nor 19b is as potent an inhibitor of prolactin secretion as its corresponding ergoline analogue, both show decreased affinity for adrenergic and serotonergic receptors, a characteristic of the ergolines.



(19)

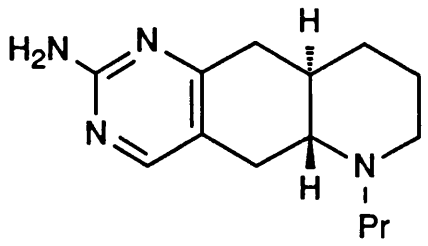


(20)

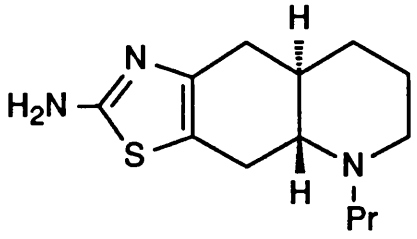
19a. $R^1=CH_2SMe$, $R^2=H$.
19b. $R^1=H$, $R^2=NHSO_2NEt_2$
19c. $R^1=R^2=H$.

Fig. 1.11.

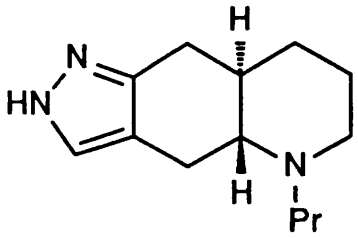
The synthesis and potent DA-2 agonist activity of LY137157 (21) and LY163792 (22, fig. 1.12) have been reported. [34] These two compounds are equipotent with pergolide at inhibiting prolactin secretion, and it is interesting to note that they display a correlation between stereochemistry and activity; the levorotatory enantiomers (as depicted) possessing all the dopaminergic activity of the racemate. A similar stereospecificity has been claimed for the pyrazole analogue LY171555 (23).[19] Clearly, the heteroaromatic rings of 21, 22 and 23 must be considered as being bioisosteric with the phenol of 19c.



(21)



(22)

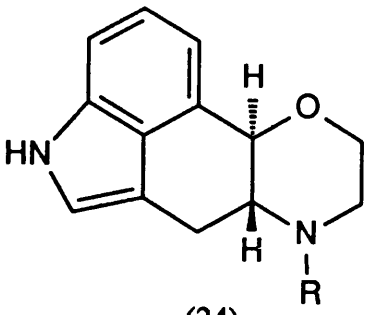


(23)

Fig. 1.12

Groups from both Merck and Roussel-Uclaf have published their work on the oxaergolines (24, fig. 1.13).[4, 35, 36] The most active analogue, 24a, has potency approximately equivalent to that of pergolide (20). A study of partial structures of EOE (24b) led workers to develop PHNO (25). [37] (+)-PHNO , the dopaminergic enantiomer, is remarkably potent at both pre- and postsynaptic DA-2 receptors, *in vivo* results including emesis in dogs. Carp retina adenylate cyclase was not stimulated by (+)-PHNO and its affinity for adrenergic and serotonergic receptors was negligible, indicating that it is a highly selective DA-2 agonist. An enantioselective synthesis of (+)-PHNO[38] has been reported recently.

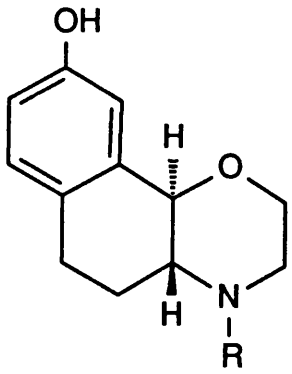
Of the heterocyclic bioisosteres coding for the phenolic moiety, the 2-thiazolamine group appears to confer the most potent dopaminergic activity to analogues. Thus, 2-thiazolamine variants have been the targets for several synthetic and SAR studies. LY163792 (22) has already been mentioned, and more recently analyses have been carried out on the aminothiazoloazepine derivative B-HT 920 (26), a compound clearly analogous to SCH-23390 (17). Anden has shown that B-



(24)

24a. R=Pr

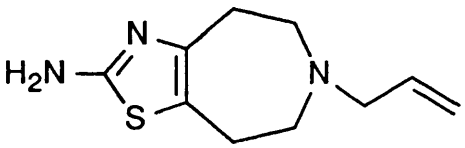
24b. R=Et



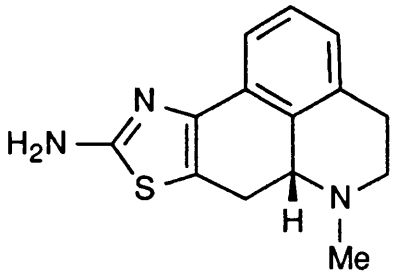
(25)

Fig. 1.13.

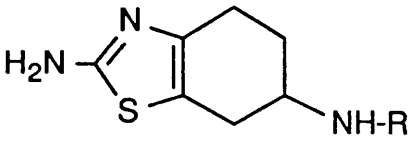
HT 920 inhibits the synthesis and α-methyltyrosine induced decline of DA in the brain of rodents. [39, 40] From these findings it was concluded that the compound is a relatively selective DA agonist that acts presynaptically.



(26)



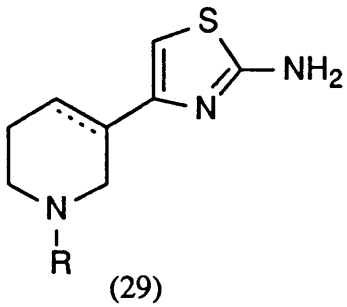
(27)



(28)

28a. R=Pr

28b. R=H



(29)

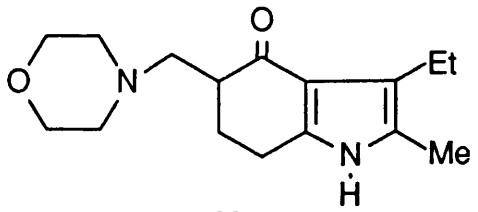
29a. R=Me

Fig. 1.14.

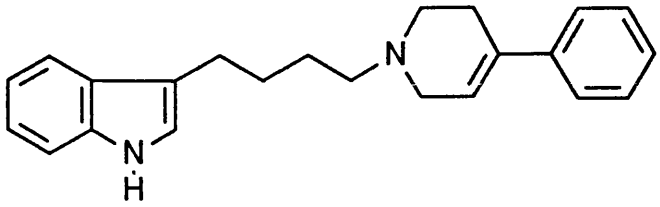
Similarly, 2-thiazolamine analogues of apomorphine (9) and the 2-aminotetralin (11) have been prepared and tested (27, 28, fig. 1.14).[41] As with apomorphine itself, the (-)enantiomer of the resolved compound (27) was found to be the most active form. (Optical resolution was accomplished using L- and D- tartaric acid, the enantiomeric tartrates being converted into the corresponding dihydrochlorides for testing). The chiral carbon 6a of (-)-27 was assumed to have the same absolute configuration of (R)-(-)-apomorphine and therefore to be R. The most active compounds of this study were, however, the enantiomers of 6-(propylamino)tetrahydrobenzo-2-thiazolamine (28a). Somewhat surprisingly, the parent compound 28b containing the primary amino function was completely inactive. An X-ray diffraction study of the L-(+)-tartaric acid salt of (-)-28b was undertaken in order to determine the absolute configuration of the amine with reference to the known configuration of L-(+)-tartaric acid. The chiral carbon in position 6 was shown to have S configuration, and this therefore established the absolute configuration of the enantiomers of 28a. Comparison of these structures revealed that (S)-28a was the most active compound, the results suggesting that in (S)-28a the 2-thiazolamine group has the appropriate orientation to invoke presynaptic activity.

In a recent patent, the Warner Lambert company have claimed the synthesis and dopaminergic activity of a group of 2-thiazolamine analogues of 3-PPP (10) (29, fig. 1.14). [42] The same compounds have been prepared and evaluated independently by workers at the Organon Scientific Development Group. Warner Lambert claim a whole range of properties for the compounds including DA agonist and antagonist behaviour, prolactin secretion inhibition and CNS activity. In the tests carried out at Organon, the most active compound was found to be (29a).

Finally, there have been some compounds discovered which exhibit potent activity and yet do not appear to fit the accepted models, or to bear a resemblance to known natural structures. These include Molindone (30), [43] which possesses DA



(30)



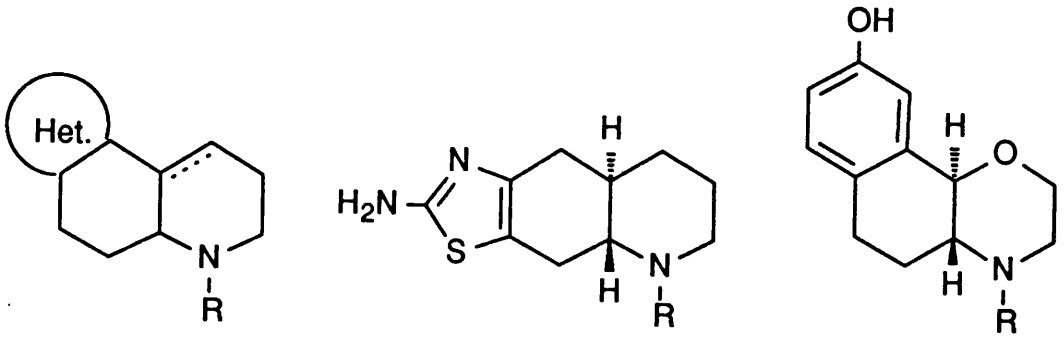
(31)

Fig. 1.15.

antagonistic, and therefore antipsychotic properties, and EMD 23-448 (31, fig. 1.15). The latter indole derivative has been described as a selective autoreceptor agonist, with activity roughly comparable to 3-PPP (10).

1.5 The Synthetic Programme.

The main objective of this project was to study methods which may be used in the preparation of compounds of the general structure (32, fig. 1.16). There is an obvious structural relationship between these compounds and known DA agonists such as LY163792 (22) and PHNO (25) (see section 1.4).



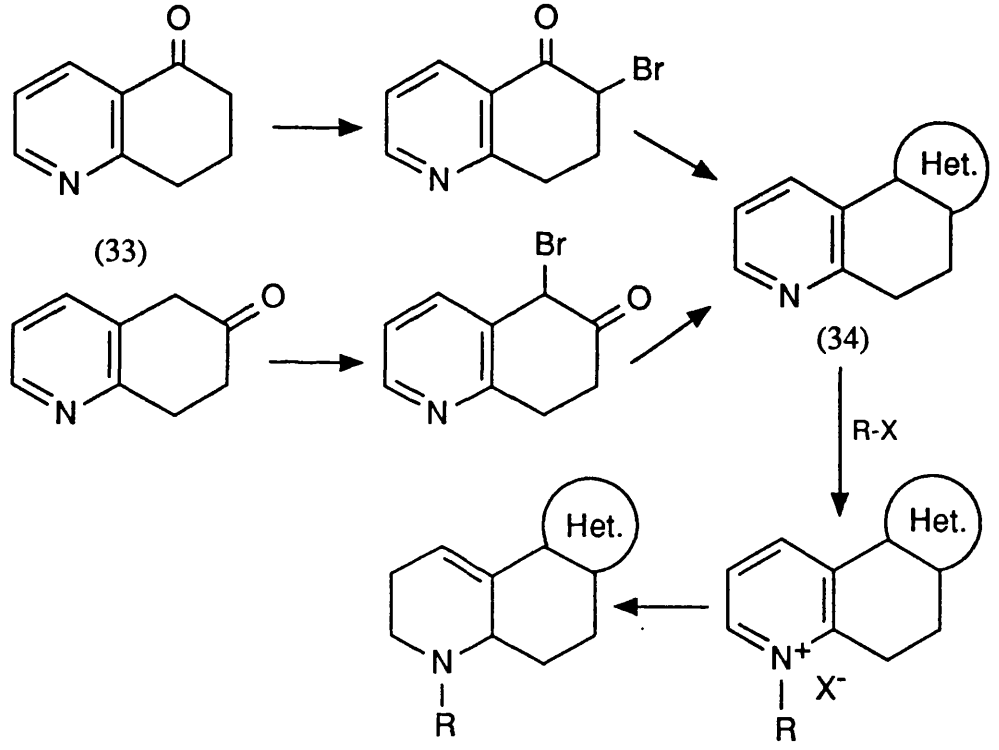
(32)
Het.=5-Membered heterocycle.

(22)

(25)

Fig. 1.16.

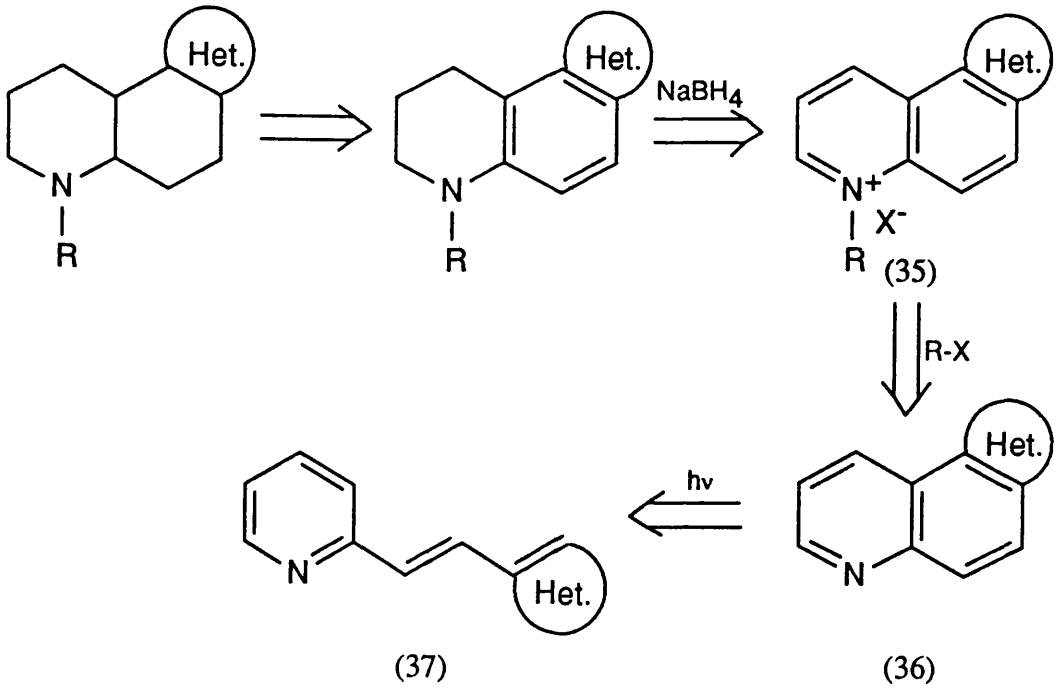
During the course of our work, the Warner Lambert company published a patent claiming the preparation of reduced quinolines of a similar type (32). In these structures the heterocyclic unit fused to the *f*-face of the quinoline may be thiazole, oxazole, pyrazole, or pyrimidine.[44] Such compounds are claimed to be active as dopamine agonists, and are therefore of importance as potential drugs for Parkinsonism or schizophrenia (see section 1.4). They were prepared *via* the route shown in scheme 1.2. The known quinolinones (33) were brominated, and the products annulated to form the tricyclic compounds (34). Quaternization provides the necessary activation to allow the reduction of the pyridine nucleus by reaction with a complex metal hydride.



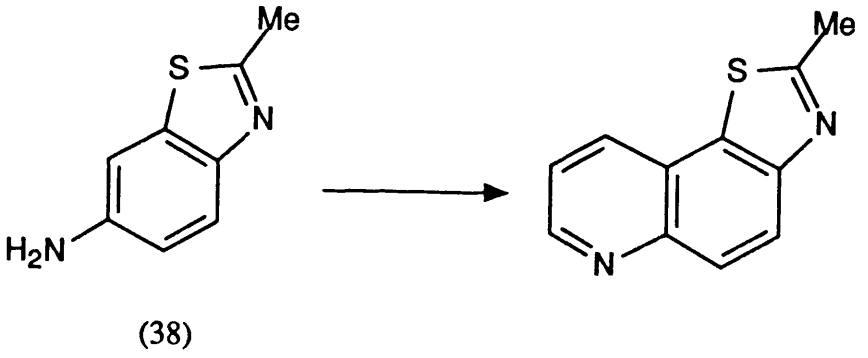
Scheme 1.2.

Our approaches to the synthesis of these compounds are illustrated by the retrosynthetic analyses in schemes 1.3 and 1.5. In the first route, the final targets are obtained by the reduction of the quaternary salts (35). The aromatic compounds (36)

are conceptually derived from the unknown heterocyclic stilbene analogues (37) *via* an oxidative photocyclisation.



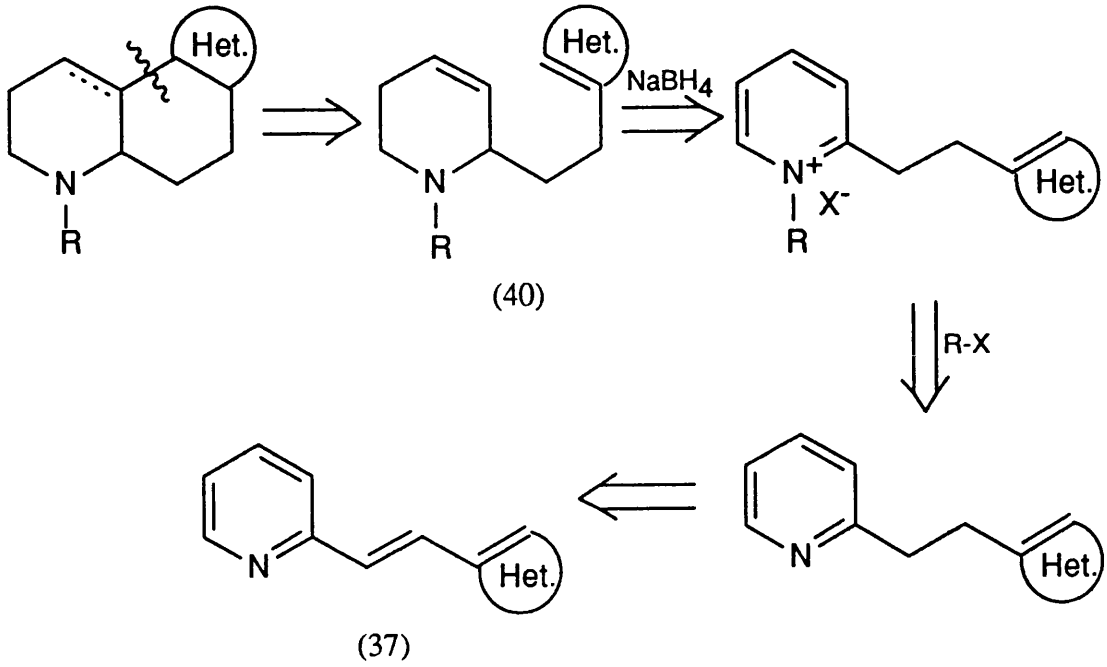
Scheme 1.3.



Scheme 1.4.

Interestingly, phenanthrene analogues of this type are known[45] and have been prepared from the corresponding amino benzothiazoles (38, scheme 1.4). In our route, however, the stilbene analogues are key intermediates since they allow entry

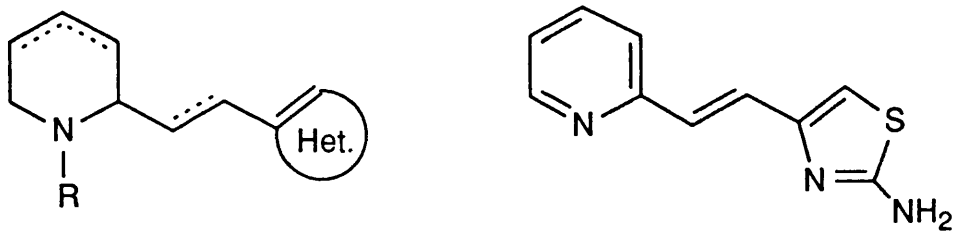
into the acyclic variants (39, fig. 1.17).



(40)

(37)

Scheme 1.5.



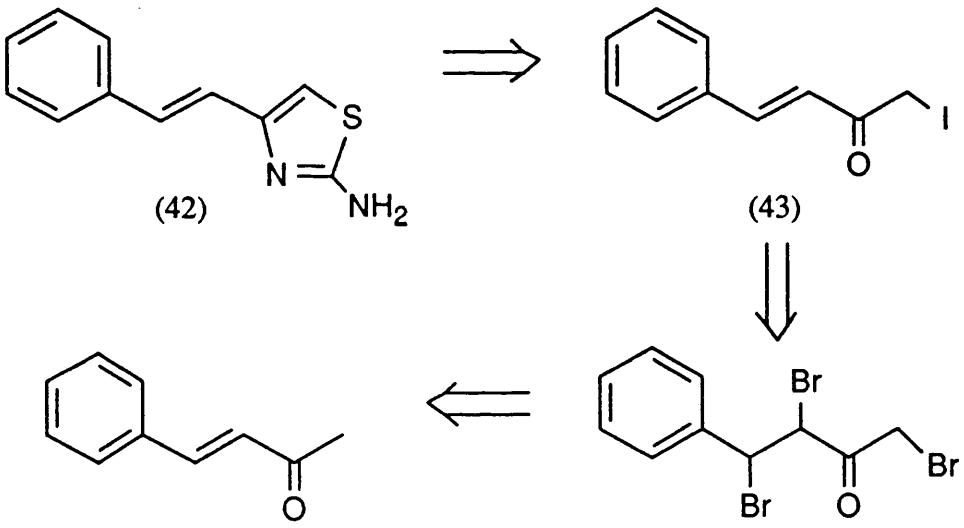
(39) (41)

Fig. 1.17.

These reduced systems, which are a completely new class of compounds, are of great importance in the second of our proposed routes (scheme 1.5). Thus, there is a key disconnection from the target compound back to the proposed 1,2,5,6-tetrahydropyridine (40) *via* an alkene-aryl coupling reaction induced by *e.g.* H^+, Br^+, Pd *etc.* A further point is that acyclic variants of structure (32), such as the tetrahydropyridines (39, fig. 1.17) might well adopt similar conformations to the

Warner Lambert compounds (32, fig. 1.16) *in vivo*, and so we continued to establish routes to them.

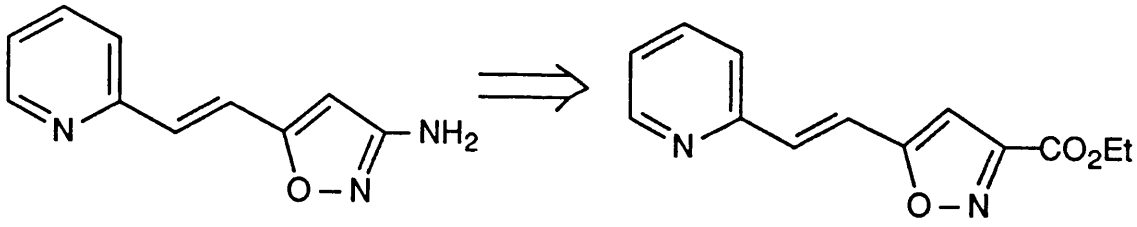
Although several different aromatic heterocyclic units which code for the dopamine aromatic ring have been prepared by other groups, we decided to concentrate our efforts on two specifically. The 2-thiazolamines were chosen, since it is known that this moiety exhibits particularly high activity in biological tests (see section 1.4). Whilst the ethenylthiazolamine (41, fig. 1.17) is unknown, the phenyl analogue (42) has been prepared from iodomethylacetophenone[46] (43), which itself was obtained from benzalacetone[47] (scheme 1.6). Although the u.v. spectra of the styrylthiazoles have been studied, there is little information regarding their chemistry.



Scheme 1.6.

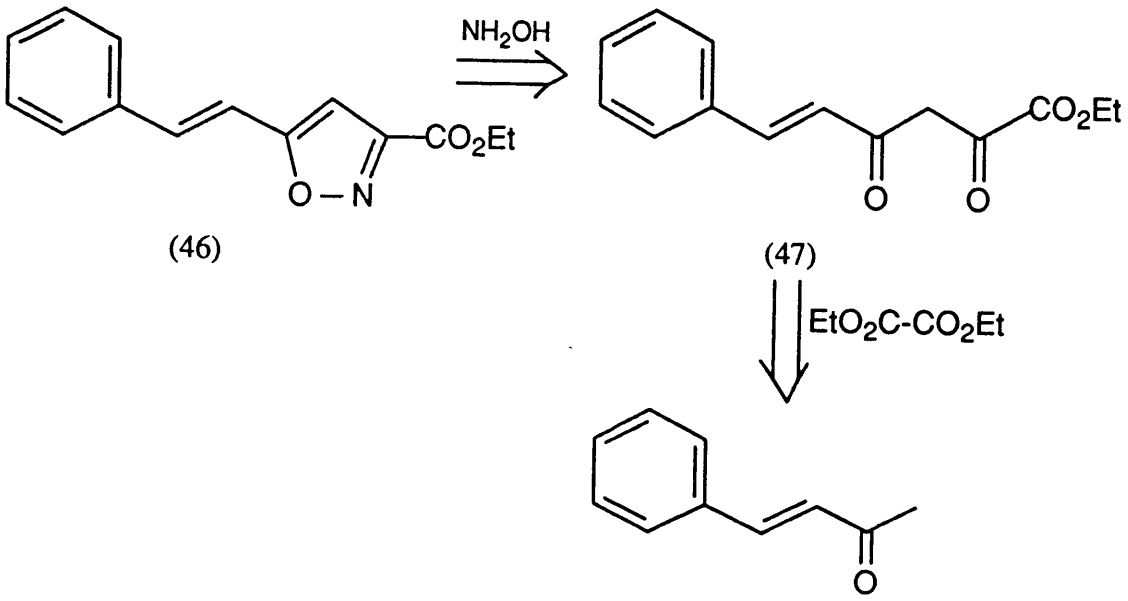
The other group of structures targeted are the isoxazoles. These are novel, and we selected the pyridoisoxazole (44, scheme 1.7) as a key intermediate. This compound was to be prepared from the ester (45), and the synthesis of this could be modelled on the production of the known analogue (46) from the β-ketoester (47),

which in turn was prepared[48, 49] from benzalacetone and diethyl oxalate (scheme 1.8).



(44) (45)

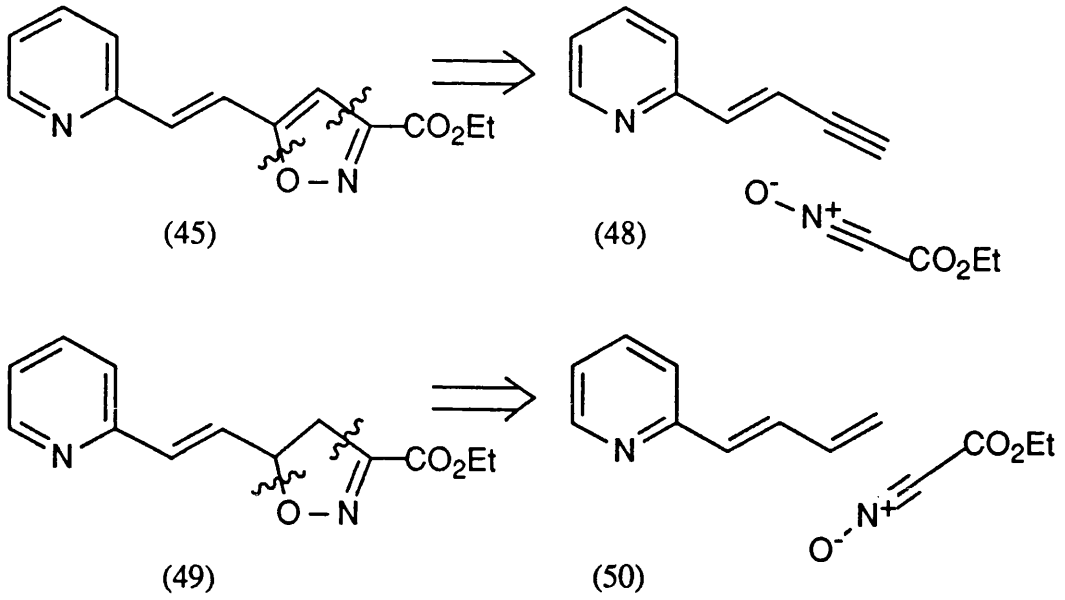
Scheme 1.7.



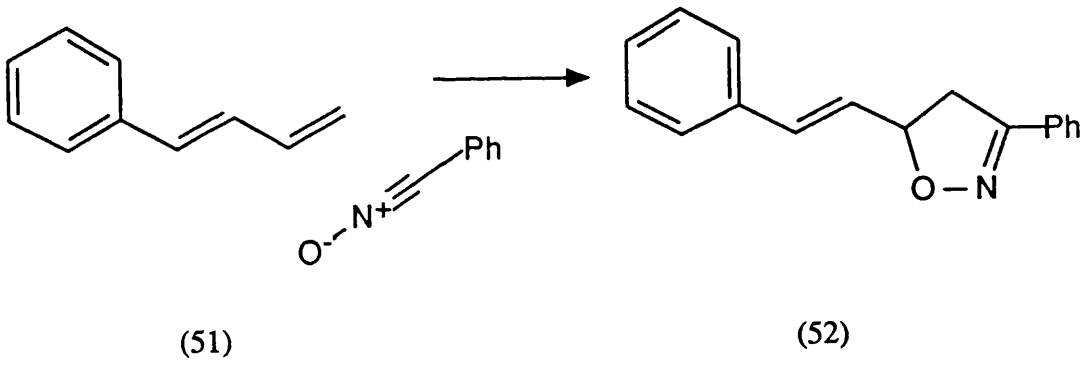
(46) (47)

Scheme 1.8.

However, rather than merely repeating this standard methodology in order to gain access to the 2-pyridyl variant (45), we decided to explore a completely different synthetic sequence. Thus, the isoxazole (45) may be disconnected back to the unknown enyne (48) and a nitrile oxide *via* a 1,3-dipolar cycloaddition (scheme 1.9). Alternatively, changing the oxidation level of the isoxazole to the isoxazoline (49) leads back to the diene (50) and a nitrile oxide. A literature precedent for these reactions is illustrated by the reaction between benzonitrile oxide and the diene (51)



Scheme 1.9.

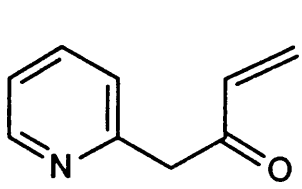


Scheme 1.10.

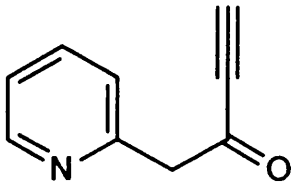
to give the isoxazoline[50, 51] (52, scheme 1.10).

Additionally, we believed that potentially more useful synthons as our primary synthetic targets were the enone (53) and the ynone (54, fig. 1.18). These compounds are likely to be even more powerful 1,3–dipolarophiles than the diene (50) and enyne (48), and therefore capable of undergoing addition with less reactive dipoles, such as nitrile sulphides and diazoacetates. Also, potential access to the thiazoles lies in the

reaction between the ynone (54) and formamidine disulphide (55, scheme 1.11).

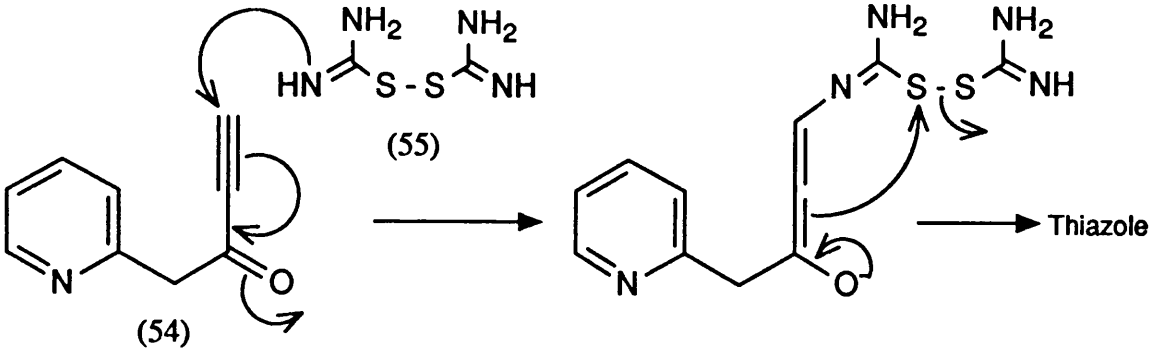


(53)



(54)

Fig. 1.18.



Scheme 1.11.

References.

1. D. E. Metzler, *Biochemistry: The Chemical Reactions of Living Cells,* Academic Press (1977).

2. E. R. Kandel and J. H. Schwartz, *The Principles of Neural Science,* Elsevier, New York, 2nd ed. (1985).

3. J. R. Cooper, F. E. Bloom, and R. H. Roth, *The Biochemical Basis of Neuropharmacology,* Oxford University Press, 5th ed. (1986).

4. J. M. Schaus and J. A. Clemens, *Annu. Rep. Med. Chem.*, 1985, **20**, 41.

5. D. Bousfield, *Neurotransmitters in action,* Elsevier, Amsterdam (1985).

6. T. Nogrady, *Medicinal Chemistry: a biochemical approach,* Oxford University Press, New York (1985).

7. M. Vance, W. Evans, and M. Thorner, *Ann. Int. Med.*, 1984, **100**, 78.

8. P. F. Spano and M. Trabucci, *Pharmacology*, 1978, **16 (suppl. 1)**, 1.

9. B. Hockfelt and S. J. Nillius, *Acta Endocrinol. (Copenhagen)*, 1978, **suppl. 216**, 1.

10. H. Wikstrom, Uppsala University, Sweden (1983).

11. A. M. Ernst, *Psychopharmacologia*, 1967 , **10**, 316.

12. N. E. Anden, K. Fuxe, T. Hockfelt, and A. Rubensson, *J. Pharm. Pharmacol.*, 1967, **19**, 627.

13. H. Wikstrom, D. Sanchez, P. Lindberg, U. Hacksell, L. E. Arvidsson, A. M. Johansson, S. O. Thorberg, J. L. G. Nilsson, K. Svensson, S. Hjorth, D. Clark, and A. Carlsson, *J. Med. Chem.*, 1984, **27**, 1030.

14. J. L. Neumeyer, W. P. Dafeldecker, B. Costall, and R. J. Naylor, *J. Med. Chem.*, 1977, **20**, 190.

15. D. D. Miller, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, 1978, **37**, 2392.

16. J. G. Cannon, J. C. Kim, and M. A. Aleem, *J. Med. Chem.*, 1972, **15**, 348.

17. D. E. Nichols, *J. Theor. Biol.*, 1976, **59**, 167.

18. N. J. Bach, E. C. Kornfeld, N. D. Jones, M. O. Chaney, D. E. Dorman, J. W. Paschal, J. A. Clemens, and E. B. Smalstig, *J. Med. Chem.*, 1980, **23**, 481.

19. R. D. Titus, E. C. Kornfeld, N. D. Jones, J. A. Clemens, E. B. Smalstig, R. W. Fuller, R. A. Hahn, M. D. Hynes, N. R. Mason, D. T. Wong, and M. M. Foreman, *J. Med. Chem.*, 1983, **26**, 1112.

20. A. Karlen, A. M. Johansson, L. Kenne, L. E. Arvidsson, and U. Hacksell, *J. Med. Chem.*, 1986, **29**, 917.

21. M. P. Seiler, A. P. Stoll, A. Closse, W. Frick, A. Jaton, and J-M. Vigouret, *J. Med. Chem.*, 1986, **29**, 912.

22. H. Wikstrom, B. Andersson, D. Sanchez, P. Lindberg, L. E. Arvidsson, A. M. Johansson, J. L. G. Nilsson, K. Svensson, S. Hjorth, and A. Carlsson, *J. Med. Chem.*, 1985, **28**, 215.

23. J. D. McDermed, G. M. McKenzie, and H. S. Freeman, *J. Med. Chem.*, 1976, **19**, 547.

24. J. McDermed, H. Freeman, and R. Ferris, *Catecholamines: Basic and Clinical Frontiers,* p. 568Pergamon , New York (1979).

25. A. Christensen, J. Arnt, J. Hyttle, J. J. Larsen, and O. Svensen, *Life Sci.*, 1984, **34**, 1529.

26. O. Gershanik, R. Heikkila, and R. Duvoisin, *Neurol.*, 1983, **33**, 1489.

27. J. Arnt and J. Hyttle, *Eur. J. Pharmacol.*, 1984, **102**, 349.

28. L. Iorio, A. Barnett, F. Leitz, V. Houser, and C. Korduba, *J. Pharmacol. Exp. Ther.*, 1983, **226**, 462.

29. H. Rosengarten, J. Schweitzer, and A. Friedhoff, *Life Sci.*, 1983, **33**, 2479.

30. Y. Itoh, M. Beaulieu, and J. Kebabian, *Eur. J. Pharmacol.*, 1984, **100**, 119.

31. K. O'Boyle and J. Waddington, *Eur. J. Pharmacol.*, 1985, **106**, 219.

32. M. Schmidt, J. Imbs, E. Geisen, and J. Schwartz, *Abstracts of "Dopamine Receptor Agonists," Philadelphia Pa.*, February 1983, abstract no. 16 .

33. R. Nordman and T. J. Petcher, *Abstracts of the 8th International Symposium on Medicinal Chemistry*, 1984, poster abstract no. 86, Uppsala, Sweden.

34. J. M. Schaus, E. C. Kornfeld, R. D. Titus, C. L. Nichols , J. A. Clemens, D. T. Wong, and E. B. Smalstig, *Abstracts of the 8th International Symposium on Medicinal Chemistry*, 1984, poster abstract no. 90, Uppsala, Sweden.

35. L. Nedec, A. Pierdet, P. Fauveau, C. Euvrard, L. Proulx-Ferland, C. Dumont, F. Labrie, and J. Boissier, *J. Med. Chem.*, 1983, **26**, 522.

36. P. S. Anderson, J. J. Baldwin, D. E. McClure, G. F. Lundell, J. H. Jones, W. C. Randall, G. E. Martin, M. Williams, J. M. Hirshfield, B. V. Clineschmidt, P. K. Lumma, and D. Remy, *J. Med. Chem.*, 1983, **26**, 363 .

37. J. H. Jones, P. S. Anderson, J. J. Baldwin, B. V. Clineschmidt, D. E. McClure, G. F. Lundell, W. C. Randall, G. E. Martin, M. Williams, J. M. Hirshfield, G. Smith, and P. K. Lumma, *J. Med. Chem.*, 1984, **27**, 1607.

38. D. G. Melillo, R. D. Larsen, D. J. Mathre, W. F. Shukis, A. W. Wood, and J. R. Colleluori, *J. Org. Chem.*, 1987, **52**, 5143.

39. N. E. Anden, H. Nilsson, E. Ros, and U. Thornstrom, *Acta Pharmacol. Toxicol.*, 1983, **52**, 51.

40. N. E. Anden, K. Golembiowska-Nikitin, and U. Thornstrom, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, 1982, **321**, 100.

41. C. S. Schneider and J. Mierau, *J. Med. Chem.*, 1987, **30**, 494.

42. J. C. Jaen, L. D. Wise, H. Tecle, and S. C. Bergmeier. (Warner-Lambert Co.), U.S. US 4 650 805.

43. E. Kyburz, *Third SCI-RSC Medicinal Chemistry Symposium* , 1985, 109, Elsevier, New York.

44. B. W. Caprathe, J. C. Jaen, and L. D. Wise. (Warner-Lambert Co.), EP 0 260 642 A2, (1987).

45. G. Di Modica, E. Barni, and F. D. Monache, *J. Heterocycl. Chem.*, 1965, **2**, 242.

46. P. L. Southwick and D. I. Sapper, *J. Org. Chem.*, 1954, **19**, 1926.

47. P. L. Southwick, L. A. Pursglove, and P. Numerof, *J. Am. Chem. Soc.*, 1950, **72**, 1604.

48. L. Rateb and G. Soliman, *J. Chem. Soc.*, 1960, 1426.

49. G. Soliman and L. Rateb, *J. Chem. Soc.*, 1956, 3663.

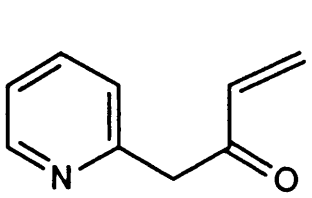
50. A. Quilico, P. Grunanger, and R. Mazzini, *Gazz. Chim. Ital.*, 1952, **82**, 349.

51. G. Lo Vecchio and P. Monforte, *Atti Soc. Peloritana*, 1957/1958, **4**, 229.

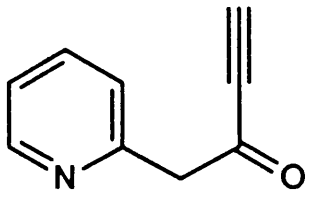
DISCUSSION AND RESULTS.

2. The Preparation of 2-Pyridylalkanols.

The initial aim of the synthetic programme was to construct a synthon capable of undergoing both 1,3-dipolar and 1,4-nucleophilic type additions, and thus lend itself to transformation to the desired heterocyclic stilbene analogues. It was therefore decided to investigate the synthesis of the α,β-unsaturated ketones 1-(2-pyridyl)-3-buten-2-one (53) and 1-(2-pyridyl)-3-butyn-2-one (54, fig. 2.1).



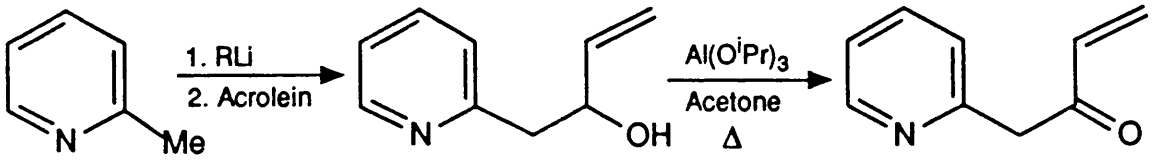
(53)



(54)

Fig. 2.1.

Whilst the ynone (54) is a novel compound, the preparation of the enone (53) has been reported.[1] This synthesis proceeds *via* a two step procedure involving the addition of acrolein to 2-picolyl-lithium to form the allylic alcohol (56) followed by an Oppenauer oxidation to give the enone (53, scheme 2.1).

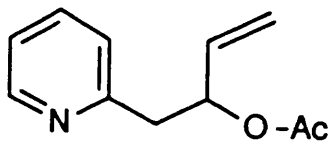


(56) (53)

Scheme 2.1.

In the author's hands the first part of this synthesis was readily repeated to afford the alcohol (56) in 54% yield. It was found that in general the formation of 2-picolyl-lithium can be accomplished using a number of different lithium bases (LDA, *n*-butyl-lithium, methyl-lithium) without affecting the outcome of the reaction. However, it was also found that THF, rather than diethyl ether, is a better solvent for the formation of the anion, its presence being detected by the deepening red colour of the solution as the base is added.

Repetition of the second step to yield the enone (53) using the reported conditions of aluminium isopropoxide in acetone heated under reflux for 12h resulted in recovery of starting material only, with no trace of the desired ketone. Changing the solvent to a higher boiling ketone (MEK) and extended periods of reflux similarly had no effect. At this point a whole range of different oxidative procedures were investigated in attempts to convert the alcohol into the enone (53). These included methods known to be fairly specific for the oxidation of allylic alcohols (such as γ-active MnO_2, PCC) as well as more general methods (Jones, Moffatt and Swern). In all cases there was either total recovery of starting material or the destruction of the molecule. The one exception to this was the Moffat conditions of DMSO-acetic anhydride at room temperature which resulted in the formation of the acylated product (57, fig. 2.2).



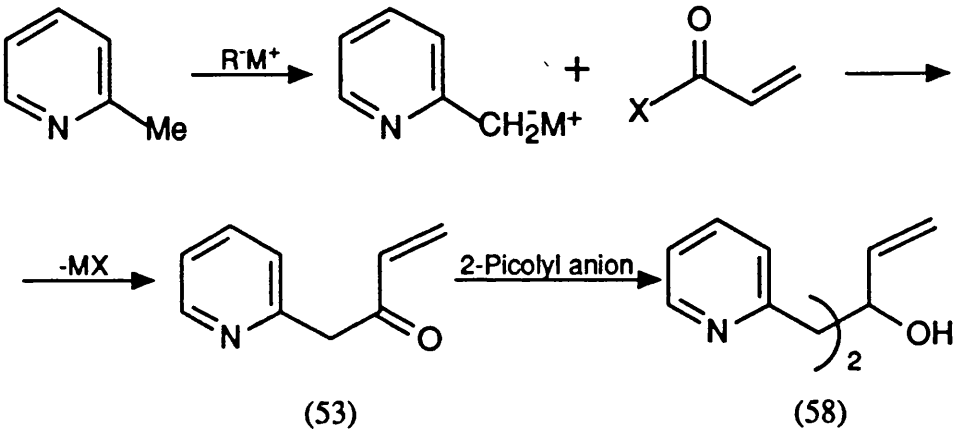
(57)

Fig. 2.2.

Inspection of the original paper by Wischmann reporting the preparation of the enone revealed that the Oppenauer oxidation was performed on 5 g of the alcohol (56) and the product was isolated by distillation. No spectral data or yield was

quoted for the product obtained and the only physical measurements recorded for either the alcohol or the enone (53) are melting and boiling points, together with elemental analyses. However, a 2,4-dinitrophenylhydrazone derivative was prepared from the enone and its melting point was reported. The omission of a yield is significant and we suspect that the productivity of the reaction is too low for its adoption in a viable synthetic sequence.

We therefore decided to approach the synthesis of the ketone *via* the displacement of a leaving group from an acryloyl moiety (scheme 2.2).

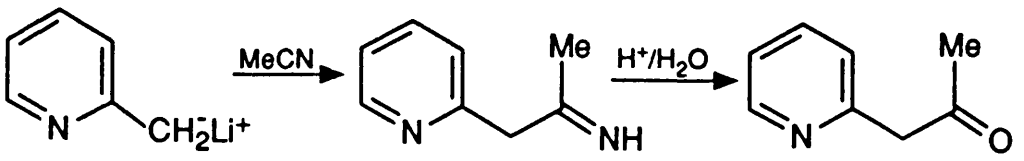


(53) (58)

Scheme 2.2.

The major problem associated with this type of reaction is undoubtedly the tendency of a second anion equivalent to attack the ketone once it is formed, resulting in formation of the tertiary alcohol (58). One way to suppress this is to react the anion with a lithium carboxylate. The intermediate dilithio species is immune to further attack by the lithium nucleophile and on hydrolysis yields the ketone. Carbanions are also known to react with nitriles forming intermediate imines which again afford the ketone on hydrolysis (scheme 2.3). For example, the reaction between 2-picolyl-lithium and acetonitrile is known to result in the isolation of 2-pyridylacetone.[2]

Treatment of the lithium salt of acrylic acid with 2-picolyl-lithium at 0°C, fol-



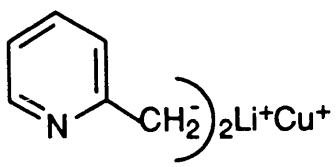
Scheme 2.3.

lowed by heating under reflux resulted in the complete recovery of starting materials; whereas acrylonitrile reacted with 2-picolyl-lithium to afford only insoluble polymeric material.

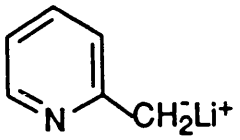
Methyl esters have been used by Levine[3] to acylate 2-picolyl-lithium, forming the corresponding ketones. In this study, two molar equivalents of anion to ester were used, on the assumption that the second step in scheme 2.4 occurs. Thus the removal of the α-pyridyl proton of the ketone (59) should suppress nucleophilic attack by a second anion equivalent. A range of methyl esters were used *i.e.* benzoate, furoate, thiophenate, acetate, propionate, isobutyrate and isovalerate. It was found that the bulky aromatic substrates reacted with 2-picolyl-lithium to form the corresponding ketones only, whilst the smaller aliphatic esters gave substantial amounts of tertiary alcohol in addition to ketone (scheme 2.4). This strongly indicated that steric bulk also played an important role in the suppression of alcohol formation. In the author's hands the treatment of methyl acrylate with 2-picolyl-lithium gave the tertiary alcohol (58) as the sole product; none of the corresponding enone (53) was isolated.

We considered that changing the leaving group to a more active species such as chloride would favour formation of the ketone in preference to the tertiary alcohol. Acyl chlorides are known to react with organometallics, forming the ketones. The organometallic species of choice in this type of reaction are lithium organocuprates and organocopper reagents (fig. 2.3). These have the advantage over organolithium

reagents in that they readily react with acyl chlorides but are generally inactive towards ketones, thus reducing the probability of alcohol formation. The disadvantage in the use of this organometallic species with α,β-unsaturated carbonyl compounds is that 1,4-addition is facilitated.



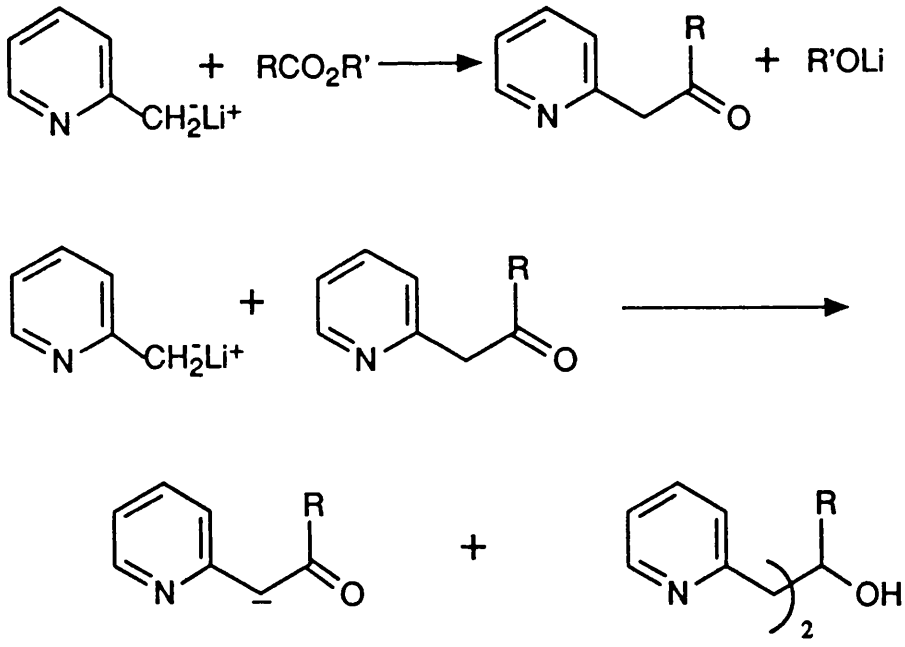
(60)



(61)

Fig. 2.3.

Lithium di-2-picolylcuprate (60) was formed by treating copper (I) iodide with 2 equivalents of 2-picolyl-lithium. This was reacted with acryloyl chloride to give an unidentified compound with complex spectral data, which may have corresponded to a 1,4 addition product. Attention was then turned to the organocopper reagent (61). The preparation of this species has been reported[4] and it has been shown to react with an acid chloride affording the corresponding ketone. Using this method, 2 equivalents of copper iodide were added to 1 equivalent of 2-picolyl-lithium and this was reacted with acryloyl chloride. A compound was isolated from this reaction which exhibited complex spectral data (the ^{1}H n.m.r. spectrum contained peaks

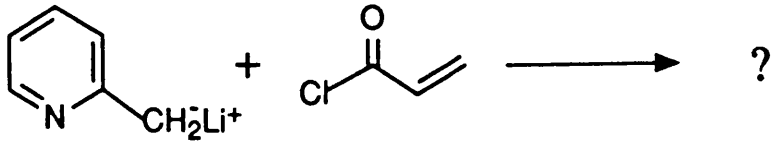


(59)

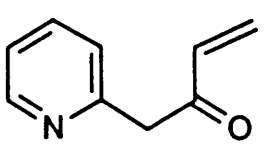
Scheme 2.4.

which appeared to correspond to pyridyl and vinyl resonances) suggesting that the reactants had combined in some way. However, it certainly was not the required ketone and repeated attempts to purify the product failed.

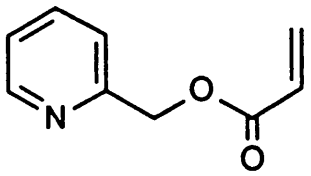
As a final attempt to prepare a pure sample of the ketone, it was decided to react 2-picolyl-lithium directly with acryloyl chloride, in the hope that this might reduce some of the side reactions occurring (scheme 2.5). In order to suppress tertiary alcohol formation, "inverse addition" was used. This technique, which requires adding the organolithium species to a solution of the electrophile, ensures that the latter is always in excess. Thus, 2-picolyl-lithium was added steadily dropwise to a cooled ether solution of acryloyl chloride. On-work up, the sole product isolated in low yield (5-8%) was an oil which was not "DNP active", but which possessed interesting spectral data. Thus the proton n.m.r. spectrum strongly indicated that this compound was the desired ketone, with the expected splitting pattern for a 2-substituted pyridine and a mono substituted vinyl unit. The resonance corresponding to that of the pyridyl α-methylene, however, appears at δ_H 5.33 which is at much lower field than would be expected for the ketone. Similarly, the ^{13}C n.m.r. spectrum possesses resonances at the correct chemical shifts for the carbon atoms of a 2-pyridyl compound attached to a vinyl ketone, except again that the peak due to the pyridyl α-methylene carbon resonance was at much lower shift than expected (δ_C 66.8). The infra red spectrum cast greater doubt on the assumption that the compound was the enone (53), as it exhibited a strong peak at $\nu_{max.}$ 1 725 cm^{-1}. It is well known that α,β-unsaturated ketones characteristically possess a carbonyl stretching band at lower wave number, usually around $\nu_{max.}$ 1 690 cm^{-1}, whilst a peak at $\nu_{max.}$ 1 725 cm^{-1} would correspond to an ester functionality. The mass spectrum was equally puzzling. Although there was a peak corresponding to the mass number of the enone (53, M^+, 147) there was also a peak of much higher intensity at m/z 163, 16 mass units greater than expected.



Scheme 2.5.



(53)



(62)

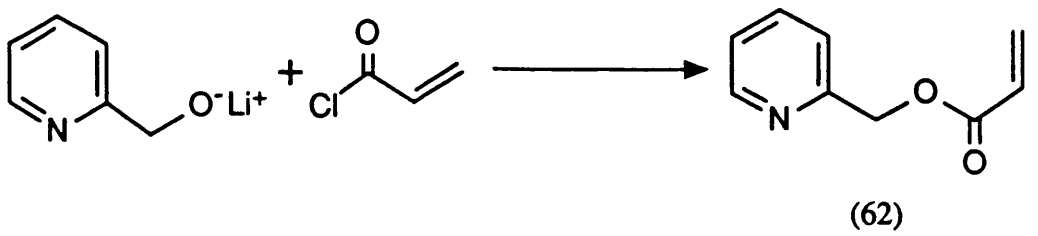
Fig. 2.4.

Consideration of all the available spectral evidence lead to the conclusion that the compound must be the ester (62, fig. 2.4). The proton and carbon resonances due to the pyridyl α-methylene unit now fit the expected values for a system of this type (table 2.1). Finally, the high resolution accurate mass spectral data provides the correct molecular formula for this product.

N.m.r. data for pyridyl α-methylene.			
	Calc. for (53).	Calc. for (62).	Found.
δ_H	3.88	5.23	5.33
δ_C	47.1	74.2	66.8

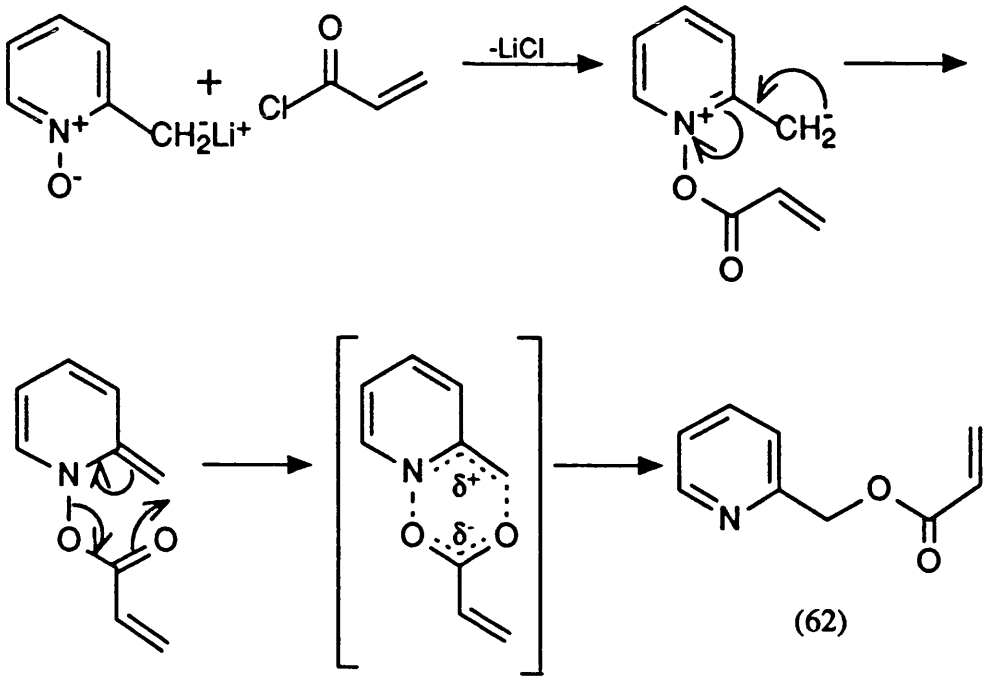
Table 2.1.

There are two likely ways that this compound may have arisen. Firstly, 2-picolyl-lithium is known to react with oxygen[5] forming lithium 2-pyridylmethoxide which is then quenched by acryloyl chloride (scheme 2.6). The second possible mechanism involves 2-picoline *N*-oxide which is present as an impurity. On *O*-acylation this may then rearrange as shown (scheme 2.7) *via* the delocalised intermediate to give the ester. The analogous reaction has been performed using acetic anhydride and 2-picoline *N*-oxide [6-8] at 100°C.



(62)

Scheme 2.6.



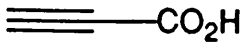
(62)

Scheme 2.7.

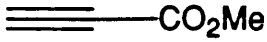
Since all attempts to form the enone had failed, it was decided to concentrate on the synthesis of the ynone (54). As has already been mentioned, this is an unknown compound and its formation was therefore of particular interest to us.

Propiolic acid (63) and methyl propiolate (64) are two readily available starting materials and these were each treated with 2-picolyl-lithium. In the former case the acid was used as the lithium carboxylate and in the latter case the ester was reacted using an inverse addition procedure. As with the analogous alkenic compounds, no identifiable products were isolated from the lithium propiolate reaction, and even the inverse addition process with the ester did not prevent the formation of the tertiary

alcohol (65, scheme 2.8).

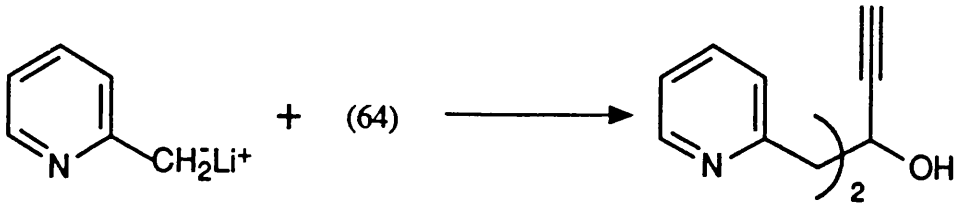


(63)



(64)

Fig. 2.5.



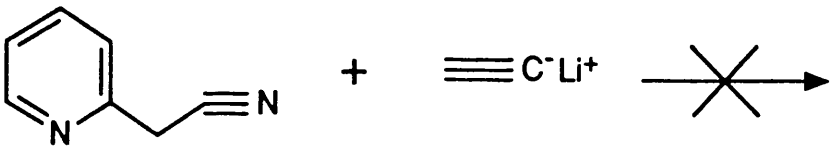
(65)

Scheme 2.8.

Propiolic acid chloride is known and is a low boiling lachrymatory liquid which fumes in air and turns yellow on standing. Consequently the compound is not easy to handle. It was prepared as quoted in the literature[9] and treated with 2-picolyl-lithium. A violent reaction occured even at very low temperatures resulting in an inseparable mixture. The reaction was therefore not pursued further.

A somewhat different approach to the synthesis of the ynone (54) was undertaken at this point. We decided to utilise the disconnection back to an acetylide synthon and 2-pyridylacetonitrile (66). Thus, monolithium acetylide (67) was formed using a literature procedure[10] and reacted with the nitrile (66, scheme 2.9). Unfortunately, work-up led to recovery of starting material. The likely reason for the lack of reactivity in this case was the labile nature of the pyridyl α-methylene protons.

Since the direct preparation of the alkynone (54) had so far failed, the obvious next step was to attempt a synthesis of the alcohol (68) and then to see whether the



(66) (67)

Scheme 2.9.

(68) (69)

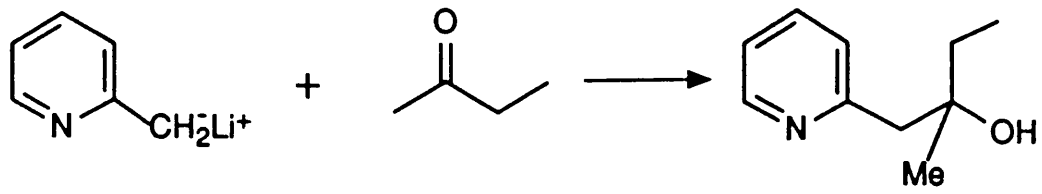
Fig. 2.6.

change from alkene to alkyne would facilitate the oxidation of the compound. It was felt that the best way to prepare this compound was *via* the aldehyde (69) and 2-picolyl-lithium.

This first required the preparation of propynal (which has recently become available commercially). Initially, however, we attempted to synthesise this compound *via* the procedure described by Veliev and Guseinov.[11] This involves the Jones oxidation of propargyl alcohol at room temperature, with MEK as the solvent, the authors claiming a 90% yield. In our hands, distillation of the residue as directed resulted in the collection of several fractions, some of which appeared to contain the aldehyde as well as MEK. (This was determined by ^{1}H n.m.r. analysis, the peak corresponding to the aldehyde proton resonance appearing at δ_H 9.2).

Since further purification appeared to be impracticable, it was decided to treat the mixture with 2-picolyl-lithium. It was hoped that by keeping the reaction temperature low, the anion would react preferentially with the more reactive aldehyde

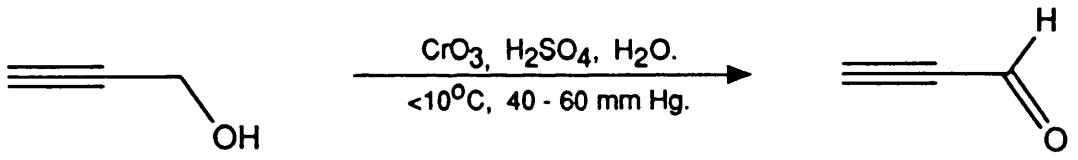
rather than the ketone. Alternatively, if both compounds reacted it might still be possible to isolate the alkynol (68).



(70) 23%

Scheme 2.10.

However, the only compound isolated from this reaction was the product resulting from the attack of 2-picolyl-lithium on MEK, *i.e.* the alcohol (70, scheme 2.10). It was therefore decided that it was not worth persisting with this particular method of propynal synthesis. Instead, an earlier method[12] was found which employs the Jones oxidation of propargyl alcohol at 2-10°C and 40-60 torr pressure, using water as the only solvent (scheme 2.11).



(69) 12.5%

Scheme 2.11.

(69) (68) 44%

Scheme 2.12.

By repeating this procedure as described, it was possible to isolate a sample of the aldehyde (69, scheme 2.11) in 12.5% yield. Reaction of this compound at -78°C with 2-picolyl-lithium resulted in isolation of the alkynol (68, scheme 2.12) as an amorphous solid which slowly decomposed at room temperature. This was a good illustration of the decreased stability of the alkyne compared to the alkene (56), which may be stored indefinitely at room temperature without decomposition.

The i.r. spectrum of the alkynol (68) clearly showed the expected bands for alkynic C-H and C≡C stretch, ($\nu_{max.}$ 3 300, 2 100 cm^{-1} respectively). Also, the ^1H n.m.r. spectrum exhibits a narrow doublet at δ_H 2.40 corresponding to the resonance of the acetylenic proton.

As with the alkenic alcohol (56), a range of oxidation procedures were carried out on the alkynol (68) but the compound was found to be resistant to all the methods attempted. At this point, therefore, it was decided to abandon our attempts to synthesise the ynone (54), and instead to elaborate the alkynol in a different manner in order to prepare compounds capable of undergoing 1,3-dipolar cycloaddition.

References.

1. K. W. Wischmann. A. V. Logan, and D. M. Stuart, *J. Org. Chem.*, 1961, **26**, 2794.

2. A. Burger and G. E. Ullyot, *J. Org. Chem.*, 1947, **12**, 342.

3. N. N. Goldberg, L. B. Barkley, and R. Levine, *J. Am. Chem. Soc.*, 1951, **73**, 4301.

4. S. Rozen, I. Shahak, and E. D. Bergmann, *Synthesis*, 1972, 701.

5. W. M. Edwards and P. C. Teague, *J. Am. Chem. Soc.*, 1949, **71**, 3548.

6. T. Cohen and G. L. Deets, *J. Am. Chem. Soc.*, 1972, **94**, 932.

7. V. J. Traynelis and Sr. A. I. Gallagher, *J. Org. Chem.*, 1970, **35**, 2792.

8. R. Bodalski and A. R. Katritzky, *J. Chem. Soc. (B)*, 1968, 83.

9. W. J. Balfour, C. C. Greig, and Somyong Visaisouk, *J. Org. Chem.*, 1974, **39**, 725.

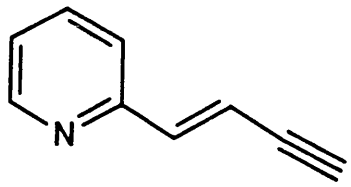
10. M. M. Midland, *J. Org. Chem.*, 1975, **40**, 2250.

11. M. G. Veliev and M. M. Guseinov, *Synthesis*, 1980, 461.

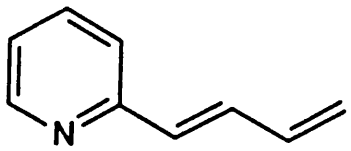
12. J. C. Sauer, *Org. Synth. Coll. Vol. 4*, 1963 , 813.

3. The Preparation of 5-[2-(2-pyridyl)ethenyl]isoxazoles.

Conjugated alkynes and alkenes are known to be powerful 1,3-dipolarophiles and it was therefore decided to investigate the chemistry of the enyne (48) and also the diene (50, fig. 3.1). Although the preparation of the 4-pyridyl enyne isomer has been reported,[1] the 2-pyridyl enyne (48) is unknown. We therefore decided to concentrate our efforts initially on the preparation of this interesting synthon.



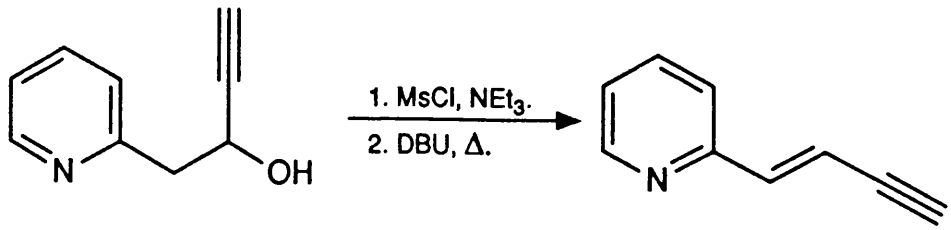
(48)



(50)

Fig. 3.1.

Treatment of the alcohol (68) with methanesulphonyl chloride, followed by elimination of the intermediate mesylate with DBU, afforded the enyne (48) in excellent yield (scheme 3.1). Analysis of the ^1H n.m.r. spectrum confirmed that it is formed as the *trans* isomer. For example, the coupling constant for the spin-spin system of the alkene protons (resonating at δ_H 6.73 and δ_H7.06) is 16 Hz. The usual limit for *transoid* coupling constants of this type is 14-18 Hz.

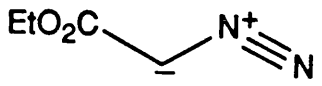


(68) (48) 99%

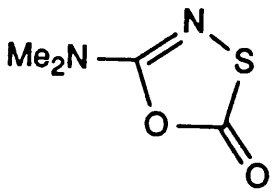
Scheme 3.1.

In order to form the required heterocycles, this product was reacted separately with ethyl diazoacetate (71) and the nitrile sulphide precursor (72, fig. 3.2).[2] In both

cases however, we found that short periods of reflux resulted in the recovery of starting materials, whilst prolonged heating caused complete decomposition. The reason for this lack of success may be that the presence of an activating carbonyl group on the dipolarophile is a prerequisite for the activation of these 1,3–dipoles in addition reactions.[3-5]



(71)

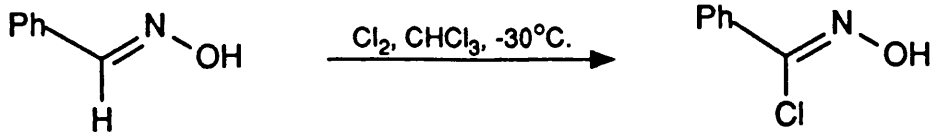


(72)

Fig. 3.2.

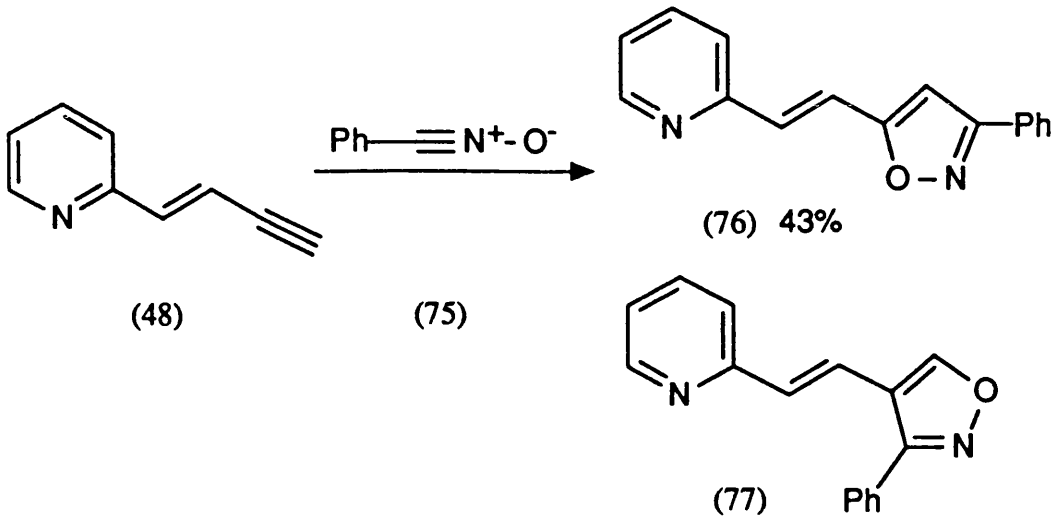
Nitrile oxides are known to be very active 1,3–dipoles[6] and as a model study, the enyne (48) and benzonitrile oxide were reacted together. Benzaldehyde oxime (73) was prepared using the method of Howe[7] in good yield and this was treated with chlorine at low temperature to afford benzohydroximinoyl chloride (74, scheme 3.2). Benzonitrile oxide (75) was generated *in situ* in the presence of the enyne (48) and the adduct (76) was isolated as a solid in reasonable yield (43%) (scheme 3.3). The ^{1}H n.m.r. spectrum of this product was particularly helpful in confirming its structure, the singlet at δ_H 6.65 corresponding to the resonance due to the isoxazole 4–H. This is in contrast to the product (77) arising from the alternative mode of attack of the nitrile oxide which would be expected to exhibit an isoxazole 5–H resonance at around δ_H 8.44 [8] (5–C is bonded to an oxygen atom). Also, the vinylic proton resonances at δ_H 7.42 and δ_H 7.63 (J 16 Hz) indicate a *trans* disubstitution pattern and confirm that the cycloaddition has occured at the triple bond. Thus, we were able to confirm that the product isolated was the 3–phenylisoxazole (76).

As this nitrile oxide dipolar addition had been successful, we decided to attempt a similar cycloaddition reaction with a nitrile oxide attached to a functional group which may be readily converted to an amino function. Primary amino isoxazoles are



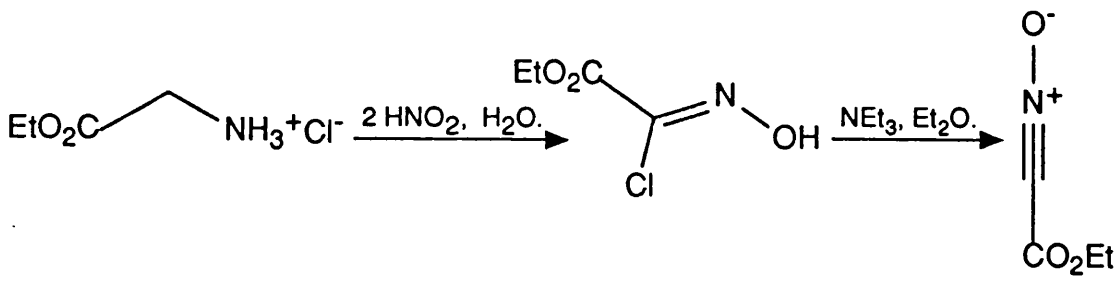
(73) (74)

Scheme 3.2.



Scheme 3.3.

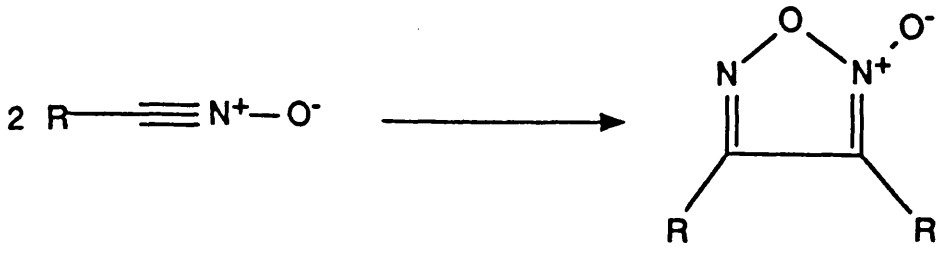
accessible *via* the Curtius rearrangement of acyl azides,[9] and thus the use of the ethyl ester nitrile oxide (78) was envisaged. This very active 1,3–dipole is generated *in situ* by the action of base on ethyl chloro–oximidoacetate (79), which in turn is prepared by the action of 2 equivalents of nitrous acid on glycine ethyl ester hydrochloride[9, 10] (80, scheme 3.4).



(80) (79) (78)

Scheme 3.4.

The main competing reaction in nitrile oxide dipolar additions is the dimerisation of the nitrile oxide to give the furoxane adduct (81), (scheme 3.5). (The presence of these compounds was indicated by t.l.c. analysis of reaction mixtures, but they were generally not isolated by the author). To overcome this competition, and therefore to ensure the maximum yield of the desired cycloadduct, 1½ equivalents of ethyl chloro–oximidoacetate were used in the reactions with the dipolarophiles.



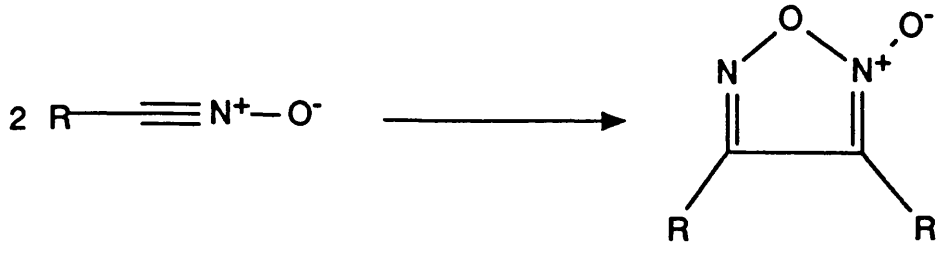
(81)

Scheme 3.5.

Typically, a dilute solution of triethylamine was added slowly to a briskly stirred ethereal solution of the enyne (48) and ethyl chloro–oximidoacetate (79), resulting in the isolation of the appropriate isoxazole (scheme 3.6). Interestingly, the yields of ethyl isoxazolecarboxylate (45) obtained (44%) were almost identical to that obtained for the preparation of the 3-phenylisoxazole (76) (43%).

As with the 1,3–dipolar addition of benzonitrile oxide to the enyne (48), only one ethyl isoxazole carboxylate isomer was isolated. This was assigned the structure (45) based on the ^{1}H and ^{13}C n.m.r. spectral data. Thus, a singlet corresponding to the isoxazole proton resonance appears at δ_H 6.74 which is characteristic of isoxazole 4-H. [Compare literature data[8] and also the spectral data already obtained for the 3-phenylisoxazole (76); the spectrum of the alternative structure (82) would show a 4-H proton resonance at *ca.* δ_H 8.44]. Doublets at δ_H 7.60 and δ_H 7.41 (J 16 Hz) correspond to the vinyl proton resonances and confirm that the cycloaddition has occured at the alkyne rather than the olefinic bond, and that the compound possesses

The main competing reaction in nitrile oxide dipolar additions is the dimerisation of the nitrile oxide to give the furoxane adduct (81), (scheme 3.5). (The presence of these compounds was indicated by t.l.c. analysis of reaction mixtures, but they were generally not isolated by the author). To overcome this competition, and therefore to ensure the maximum yield of the desired cycloadduct, 1½ equivalents of ethyl chloro–oximidoacetate were used in the reactions with the dipolarophiles.

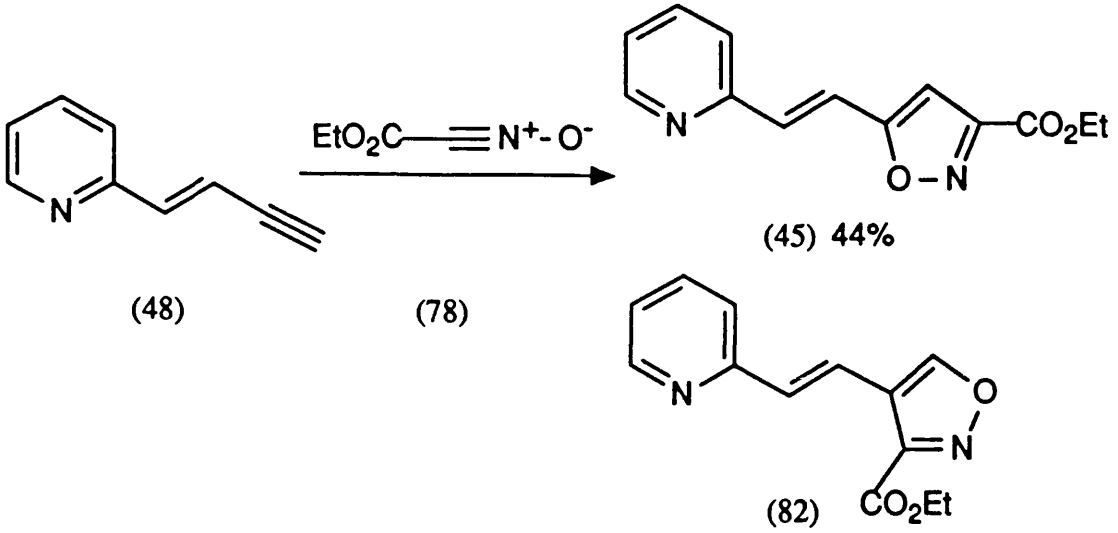


(81)

Scheme 3.5.

Typically, a dilute solution of triethylamine was added slowly to a briskly stirred ethereal solution of the enyne (48) and ethyl chloro–oximidoacetate (79), resulting in the isolation of the appropriate isoxazole (scheme 3.6). Interestingly, the yields of ethyl isoxazolecarboxylate (45) obtained (44%) were almost identical to that obtained for the preparation of the 3–phenylisoxazole (76) (43%).

As with the 1,3–dipolar addition of benzonitrile oxide to the enyne (48), only one ethyl isoxazole carboxylate isomer was isolated. This was assigned the structure (45) based on the ^{1}H and ^{13}C n.m.r. spectral data. Thus, a singlet corresponding to the isoxazole proton resonance appears at δ_H 6.74 which is characteristic of isoxazole 4–H. [Compare literature data[8] and also the spectral data already obtained for the 3–phenylisoxazole (76); the spectrum of the alternative structure (82) would show a 4–H proton resonance at *ca.* δ_H 8.44]. Doublets at δ_H 7.60 and δ_H 7.41 (J 16 Hz) correspond to the vinyl proton resonances and confirm that the cycloaddition has occured at the alkyne rather than the olefinic bond, and that the compound possesses

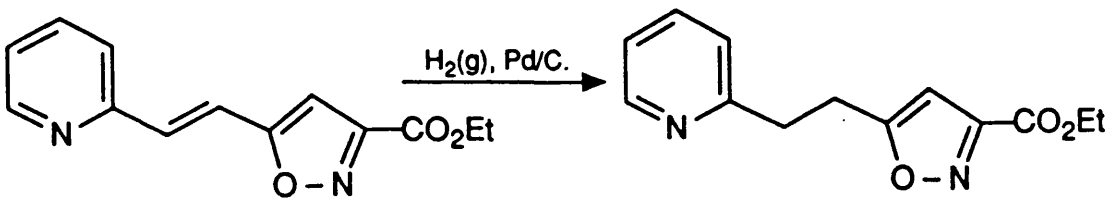


Scheme 3.6.

a *trans* di-substituted vinylic unit. The ^{13}C n.m.r. spectrum exhibits a doublet at δ_C 103.1 corresponding to the resonance due to 4-C, whilst the singlets at δ_C 156.7 and δ_C 159.8 are due to the resonances of 5-C and 3-C respectively. This is in contrast to the spectrum of the other regioisomer (82) in which the carbon at position 5 would be expected to resonate as a doublet at $\approx \delta_C$ 158, and 3-C and 4-C would appear as singlets resonating at *ca.* δ_C 149 and δ_C 104 respectively.[11]

In order to prove that our assignments are correct for this structure, the vinyl group was hydrogenated to furnish the ethylisoxazole (83, scheme 3.7). [Although this is also a well known method for the cleavage of isoxazole N-O bonds,[12] it was interesting to note that in our hands even at relatively high hydrogenation pressure (18 atmospheres) the isoxazole portion of the molecule was found to remain intact]. In the ^1H n.m.r. spectrum of this non-conjugated isoxazole, the 4-H resonance appears as a singlet at δ_H 6.40, and the methine carbon at that position resonates at δ_C 101.7 in the carbon spectrum. The quaternary carbons 3-C and 5-C produce signals at δ_C 158.8 and δ_C 156.2 respectively, in accordance with the assigned structure.

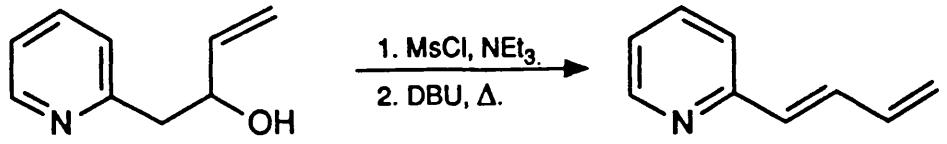
Our success with nitrile oxide cycloadditons to the enyne (48) prompted an investigation of the properties of the diene (50) as a dipolarophile. The compound is



(45) (83) 85%

Scheme 3.7.

known[13,14] and in the author's hands it was readily obtained in quantitative yield *via* mesylation and elimination of the alcohol (56, scheme 3.8).

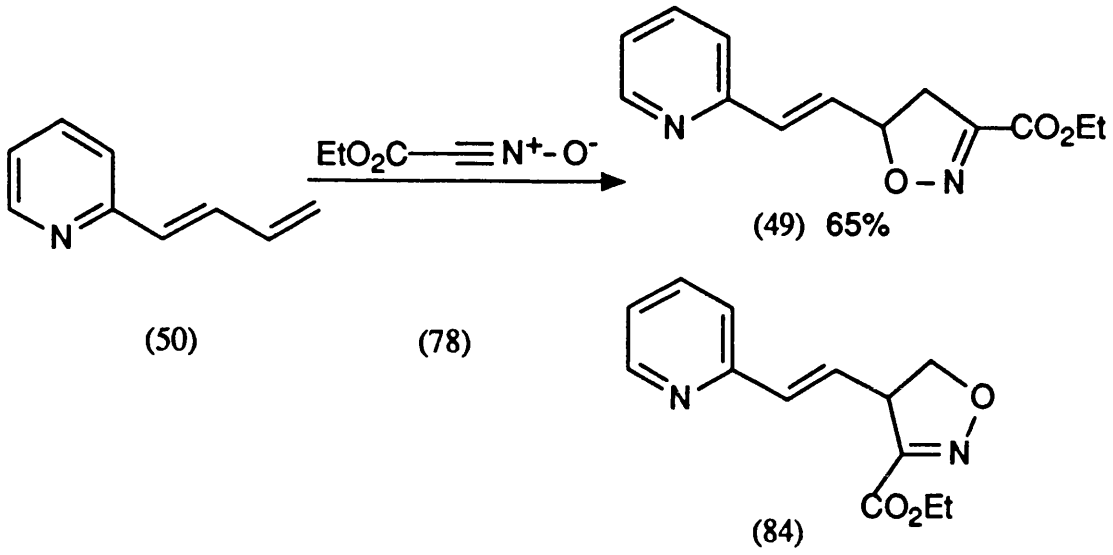


(56) (50) 72%

Scheme 3.8.

Treatment of the diene (50) with the nitrile oxide (78) in identical fashion to that used for the enyne (48) resulted in the isolation after work-up of a single product in 65% yield, (scheme 3.9).

Once again, it was possible to elucidate the structure of this compound by examination of its n.m.r. spectra. Firstly, that the addition had taken place at the terminal olefin was indicated by the pair of doublets in the ^{1}H n.m.r. spectrum at δ_H 6.73 and δ_H 6.80 (J 16 Hz) corresponding to the resonances of the vinylic protons 1'-H and 2'-H. Secondly, there are two possible isoxazolines which may arise from cycloaddition at the terminal bond, (49) and (84). The proton n.m.r. spectrum of our isoxazoline exhibits a multiplet at δ_H 5.46 and doubled doublets at δ_H 3.17 and δ_H 3.46. Examination of the chemical shifts of these signals led us to believe that the downfield multiplet must arise from the resonance of a proton adjacent to the isoxa-

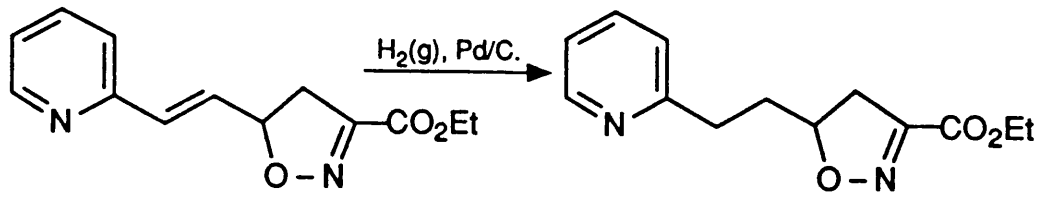


Scheme 3.9.

zoline oxygen, whereas the doubled doublets, resulting from the resonances of the geminal pair, appear upfield by ≈ 2 p.p.m. This indicates that these protons are far less deshielded than the proton at position 5, and hence must be adjacent to the isoxazoline C=N unit. Thus the structural assignment (49) would fit the ^{1}H n.m.r. spectral information.

Finally, the ^{13}C n.m.r. spectrum provides the most convincing evidence that the nitrile oxide addition has occured to afford the regioisomer (49). Thus the triplet at δ_C 39.1 corresponds to the signal produced by the methylene unit 4-C, and the doublet at δ_C 83.3 is due to the resonance of the methine carbon at position 5.

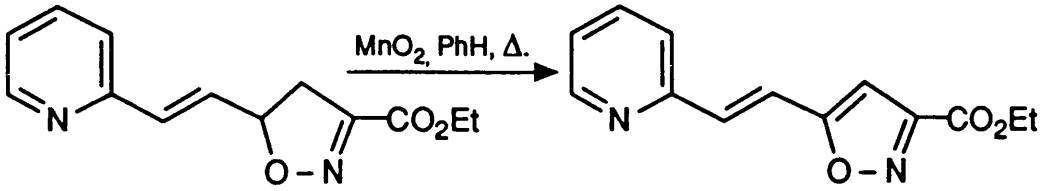
With the correctly assigned isoxazoline (49) to hand, we decided to investigate the properties of the compound with respect to its reduction and oxidation.



(49) (85) 86%

Scheme 3.10.

The vinyl unit of the isoxazoline (49) was hydrogenated, [H_2 (gas), Pd/C (cat.)], to yield the ethylisoxazoline (85, scheme 3.10). This compound was subjected to conditions which are known in some cases to result in cleavage of the isoxazoline N-O bond, [H_2 (gas), PtO_2 (cat.), AcOH]. [12] Interestingly however, as with the ethylisoxazole (83) starting material only was isolated.

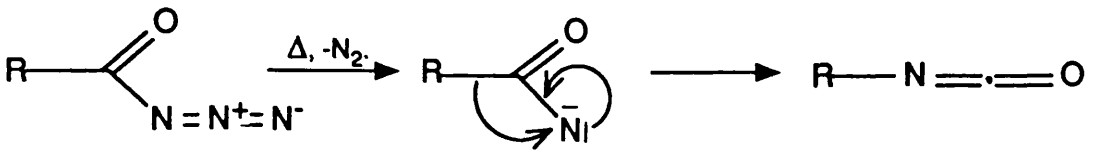


(49) (45) 67%

Scheme 3.11.

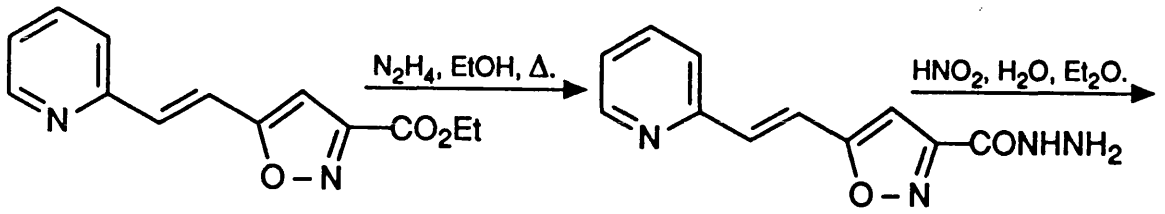
The aromatisation of isoxazolines to isoxazoles may be accomplished using γ-active MnO_2 as the dehydrogenating agent.[15] Thus, we found that the isoxazoline (49) may be heated under reflux with MnO_2 in dry benzene to afford a single product in high yield (scheme 3.11). The spectral and physical data for this compound are identical to that of the isoxazole (45) derived from the addition of the nitrile oxide (78) to the enyne (48). This not only provided a corroborative piece of evidence justifying our earlier assignment of the regiochemistry of the cycloadditions, but also demonstrated that we now had a viable and complementary second synthetic route to the stilbene analogue (45).

It was at this point that we decided to perform the Curtius reaction on our new compound, in order to obtain the 3-isoxazolamine (44, scheme 1.7, p. 26), protected as the carbamate. Acyl azides may be obtained by the action of nitrous acid on hydrazides,[16] which in turn are prepared from hydrazine and an ester. Heating the acyl azide in a suitable solvent causes the formation of an intermediate acyl nitrene which rearranges to give an isocyanate (86, scheme 3.12). If the reaction is carried out in an alcohol as the solvent, then the product isolated is the corresponding carba-

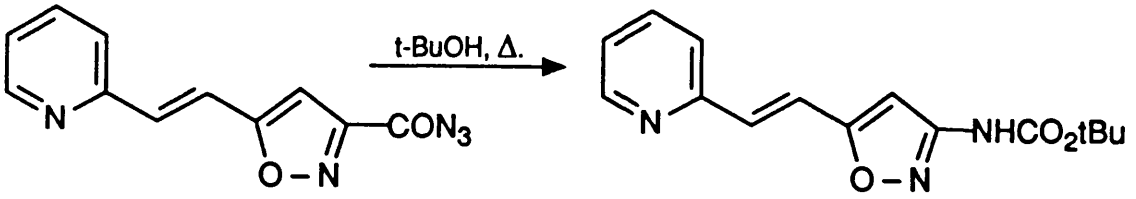


(86)

Scheme 3.12.



(45) (87) 35%



(88) 75% (89) 57%

Scheme 3.13.

mate.

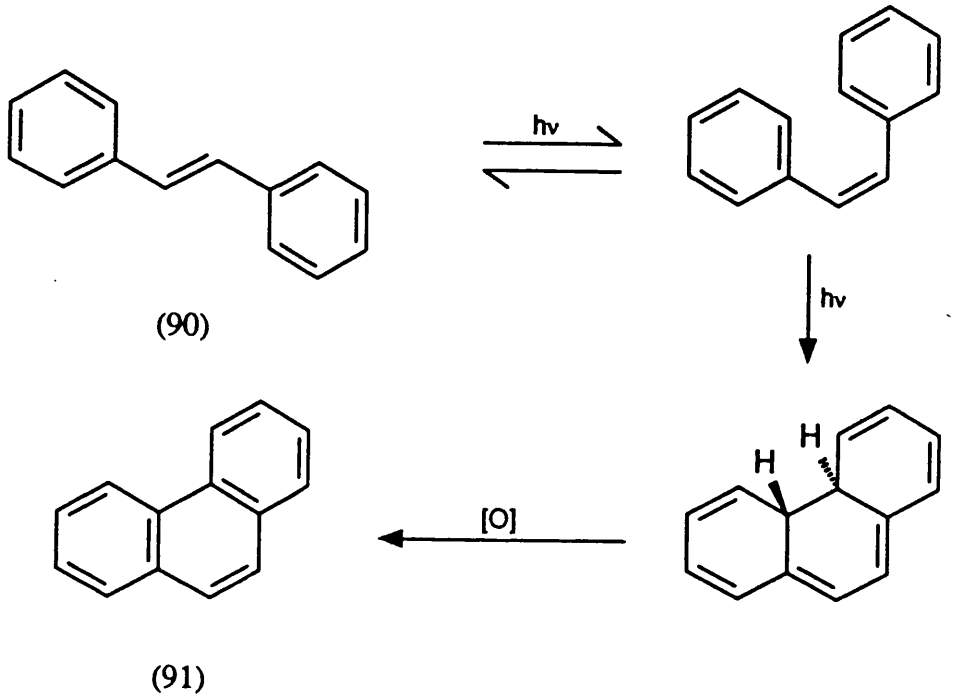
We found that heating the isoxazole (45) with hydrazine in ethanol yielded the hydrazide (87,scheme 3.13). This was then treated with nitrous acid at ice bath temperature to afford the acyl azide (88), which was heated under reflux in *t*-butanol to effect rearrangement to the *t*-butyl carbamate (89). Hence we have demonstrated that this is a convenient route for the preparation of 3-amino derivatives of our isoxazole stilbene analogue (45). Further, it was now possible for us to use these compounds as substrates for photochemical cyclisation reactions.

References.

1. K. Eiter and H. Oediger, *Ann. Chem.*, 1965, **682**, 62.
2. I. T. Hogan and M. Sainsbury, *Tetrahedron*, 1984, **40**, 681.
3. R. K. Howe, T. A. Gruner, L. G. Carter, L. L. Black, and J. E. Frantz, *J. Org. Chem.*, 1978, **43**, 3736.
4. R. K. Howe and J. E. Frantz, *J. Org. Chem.*, 1978, **43**, 3742.
5. M. J. Sanders and J. R. Grunwell, *J. Org. Chem.*, 1980, **45**, 3753.
6. C. Grundmann and P. Grunanger, *The Nitrile Oxides,* Springer Verlag, New York (1971).
7. Kou-Chang Liu, B. R. Shelton, and R. K. Howe, *J. Org. Chem.*, 1980, **45**, 3916.
8. S. D. Sokolov, I. M. Yudinseva, and P. V. Petrovskii, *Zh. Org. Khim*, 1970, **6**, 2584.
9. M. Freri and G. S. Skinner, *J. Am. Chem. Soc.*, 1924, **46**, 731.
10. A. P. Kozikowski and M. Adamczyk, *J. Org. Chem.*, 1983, **48**, 366.
11. J. Gainer , *Org. Magn. Reson.*, 1976, **8**, 226.
12. M. Ihara, F. Konno, and K. Fukumoto, *Heterocycles*, 1983, **20**, 2181.
13. E. Profft and H-W. Linke, *Chem. Ber.*, 1960, **93**, 2591.
14. B. I. Rosen and W. P. Weber, *J. Org. Chem.*, 1977, **42**, 47.
15. A. Barco, S. Benetti, and G. P. Pollini. *Synthesis*, 1977, 837.
16. P. A. S. Smith, *Org. React.*, 1946, **3**, 337.

4. The Preparation and Photochemistry of Heterocyclic Stilbene Analogues.

The photocyclodehydrogenation of stilbene (90, scheme 4.1) was first observed by Smakula[1] in 1934 although the reaction product was not identified as phenanthrene (91) until 1950.[2] This 6 π electron conrotatory electrocyclic ring closure, followed by an *in situ* oxidation of an intermediary dihydrophenanthrene, has been thoroughly studied and synthetically is one of the most useful photochemical reactions.

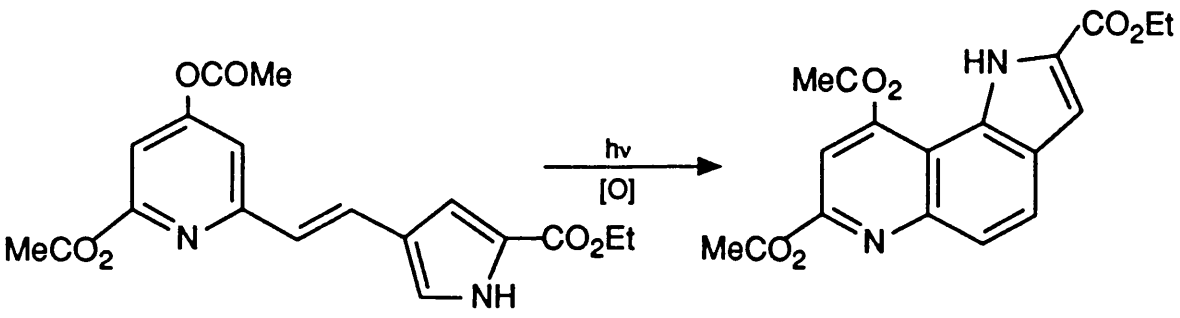


(90)

(91)

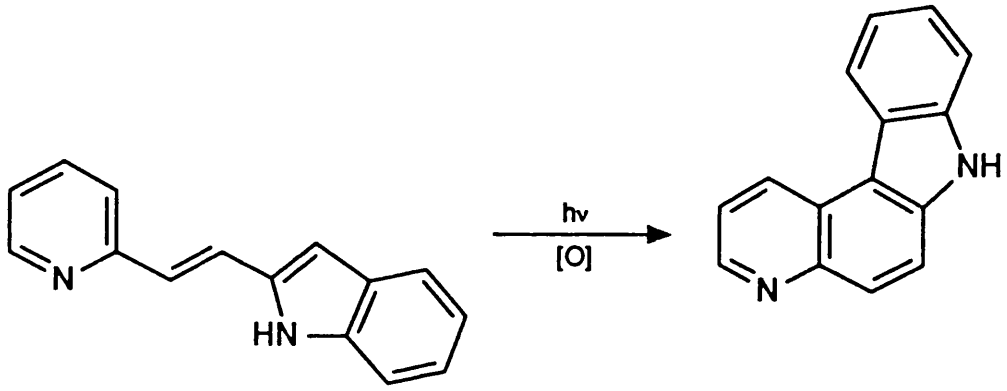
Scheme 4.1.

Some heterocyclic analogues of stilbene are also known to undergo this reaction, although the yields are usually lower.[3,4] For example, in a recent synthesis of the coenzyme methoxatin[5] the key step is a photocyclisation of the compound (92) to yield the triester (93, scheme 4.2) in 46% yield. Snieckus has similarly effected the photocyclisation of the pyridyl-indolyl stilbene analogue[6] (94, scheme 4.3). Peculiarly, it was found that the 2-pyridyl-3-indolyl stilbene (95) failed to photocyclise

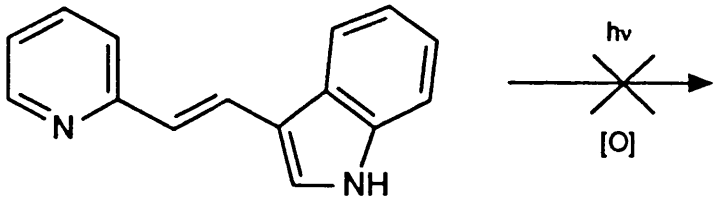


(92) (93)

Scheme 4.2.

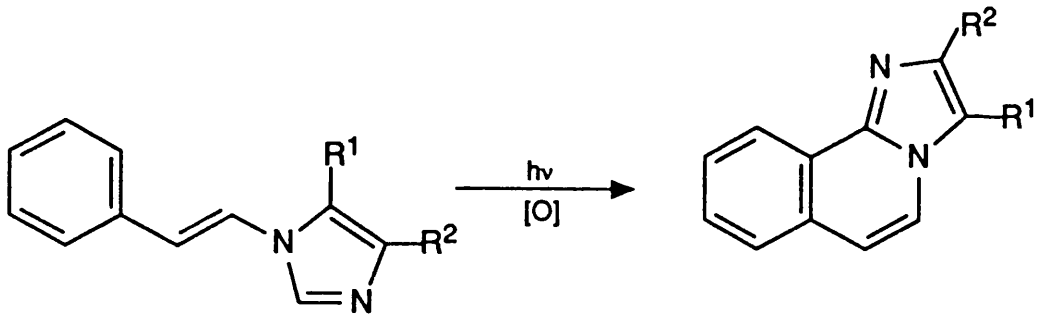


(94)



(95)

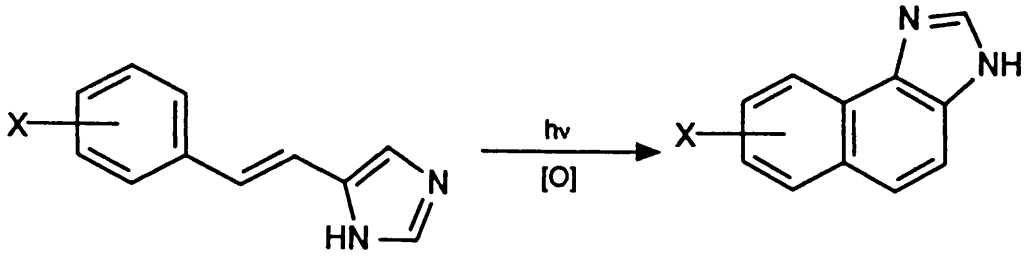
Scheme 4.3.



(96) (97)

Scheme 4.4.

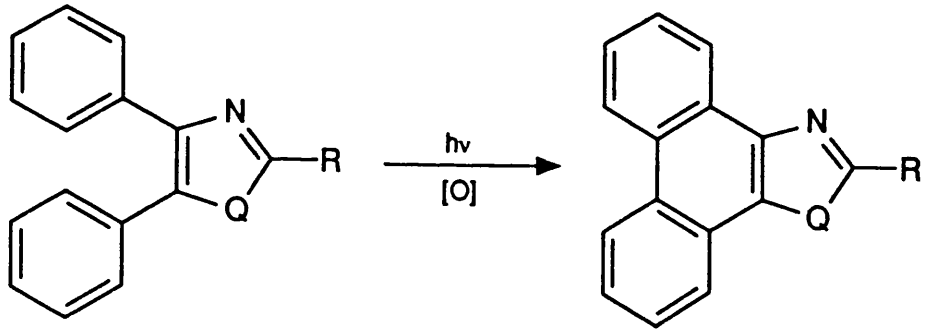
under conditions which are successful for its analogues.[7] Some stilbene analogues with 5-membered rings containing more than one heteroatom have been successfully cyclised photochemically. 1-Styrylimidazole (96) and some of its derivatives were converted to the corresponding phenanthrene analogues under photochemical conditions (scheme 4.4).[8] Another example of this type of chemistry was demonstrated by Swedish workers[9] who were able to oxidatively cyclise the isomeric 4-(arylethenyl)imidazoles (98, scheme 4.5). Finally, Wasserman has reported that a range of compounds of the general structure (99) are cyclised by photochemical means to yield the products (100, scheme 4.6).[10]



(98)

X=H, Me, NO_2, Cl.

Scheme 4.5.



(99) (100)

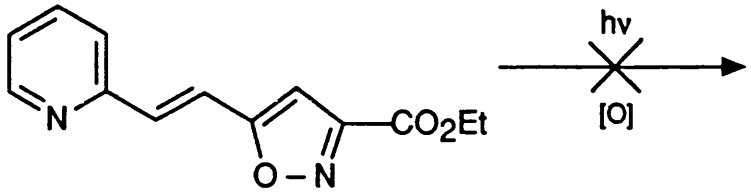
Q=O, S, NR^1.

R=Me, H, Ph

Scheme 4.6.

We believed that a similar electrocyclic ring closure might be accomplished with our pyridylisoxazole stilbene analogue (45). The conditions we used initially to effect the transformation were quite standard for this type of reaction: a 400 W medium

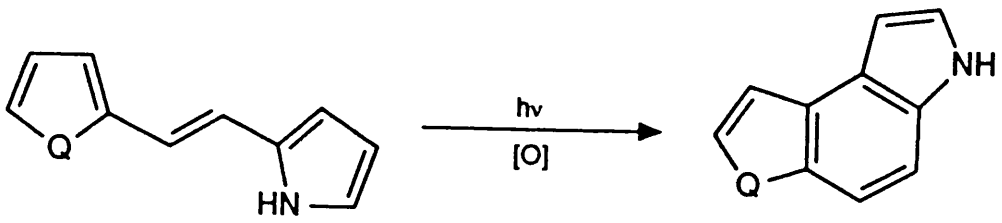
pressure mercury lamp within a water-cooled photochemical reactor, the substrate dissolved in benzene, with a trace of iodine as the oxidant. Under these conditions (scheme 4.7), however, a complex mixture was obtained. A similar result occurred in an experiment using a Pyrex immersion well to filter out some of the radiation.



(45)

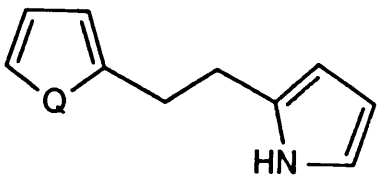
Scheme 4.7.

A particularly mild set of conditions for the photocyclisation of heterocyclic stilbene analogues have been described by Cava.[11,12] In this study, the authors found that substrates containing electron-rich heterocycles were easily destroyed by oxidants. A range of pyrrolylstilbenes (101, scheme 4.8) were photocyclised using palladium on charcoal as the oxidant. *p*-Nitrobenzoic acid/triethylamine was also added to the reaction mixture as a hydrogen acceptor, preventing the competing hydrogen transfer reaction of the starting material to give the reduced adducts (102).



(101)

Q=NH, O, S etc.

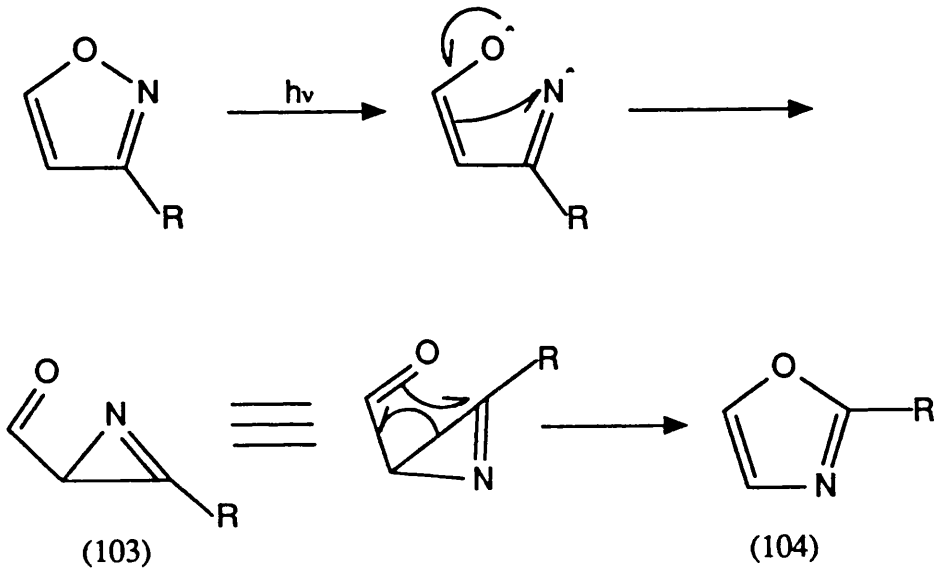


(102)

Scheme 4.8.

When we subjected our pyridylisoxazole substrate (45) to these conditions however, irradiation for 18h led to the complete destruction of the molecule. The experiment was repeated and this time the course of the reaction was followed by t.l.c. analysis. This indicated the slow disappearance of starting material but after 8h attempted purification of the reaction mixture by column chromatography afforded no identifiable products.

It was our opinion that the lack of success we had experienced thus far was attributable to the isoxazole N-O bond in our substrate. Isoxazoles are known to undergo photolytic cleavage and subsequently rearrange to the corresponding oxazole (104) *via* an intermediate azirine (103, scheme 4.9). This reaction, as well as other photorearrangements and reactions with solvent molecules presumably participates in the degradation of the compound (45).



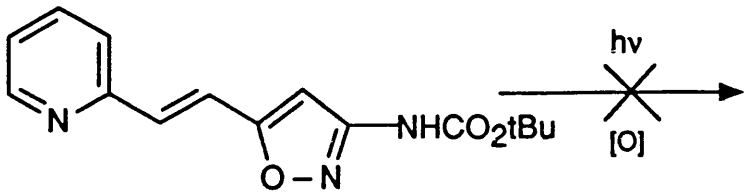
(103) (104)

Scheme 4.9.

We surmised that changing the ethyl carboxylate group at 3-C of the isoxazole to a different functional group would alter the electronic nature of the system and facilitate the desired photocyclisation. An obvious choice of functional group was a primary amino moiety, since we were particularly interested in these derivatives. Fortunately, we had already obtained the relevant 3-isoxazolamine protected as the

t-butyl carbamate (89) *via* a Curtius rearrangement.

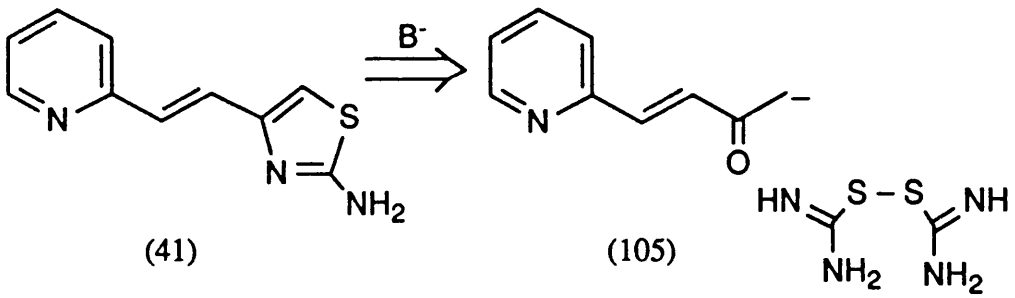
The isoxazolamine carbamate (89, scheme 4.10) was irradiated with a 400 W medium pressure lamp in benzene-methanol (3:1) for 8h. However, as with the ethyl isoxazolecarboxylate photolysis of the substrate had occurred, and chromatographic separation of the reaction mixture gave unidentified decomposition products only.



(89)

Scheme 4.10.

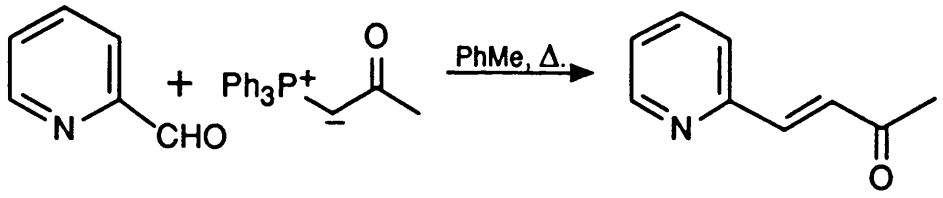
It was at this point that we decided that the isoxazole ring is too susceptible to photoisomerism and cleavage to be a viable substrate for photochemical cyclisation. We therefore turned our attention to the ethenylthiazolamine (41) in the hope that this compound would prove to be stable to the conditions employed in the photocyclic reaction. This first required the preparation of the stilbene analogue (41), a hitherto unknown compound. Retrosynthetic analysis indicates that it may be prepared from the enone (105) and formamidine disulphide (55) under basic conditions (scheme 4.11).



(41) (105) (55)

Scheme 4.11.

The 2-pyridylenone (105) is known[13] and was prepared *via* the reaction of 2-pyridinecarboxaldehyde (106) and triphenylphosphoranylidene-2-propanone (scheme 4.12), as described in the literature.

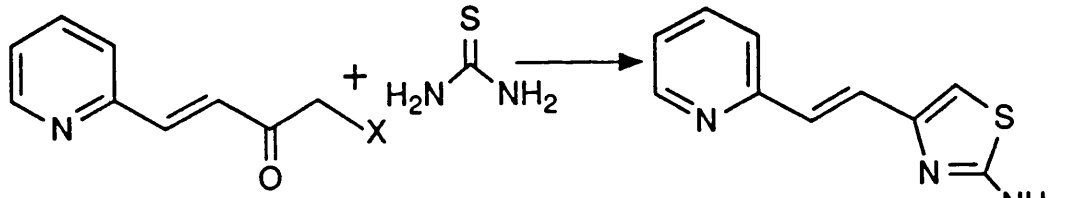


(106) (105) 81%

Scheme 4.12.

Heating the enone (105) with formamidine disulphide dihydrochloride in the presence of sodium bicarbonate, according to the method of King,[14-16] resulted in the formation of an intractible black tar. Similarly, *in situ* generation of formamidine disulphide (55) using iodine and thiourea in dioxane at reflux temperature[17] gave an inseparable mixture.

Since these methods of thiazole formation had been unsuccessful, we considered that the preparation of the halomethylenone (106, scheme 4.13) followed by treatment with thiourea would be a viable route to the new 2-thiazolamine (41).

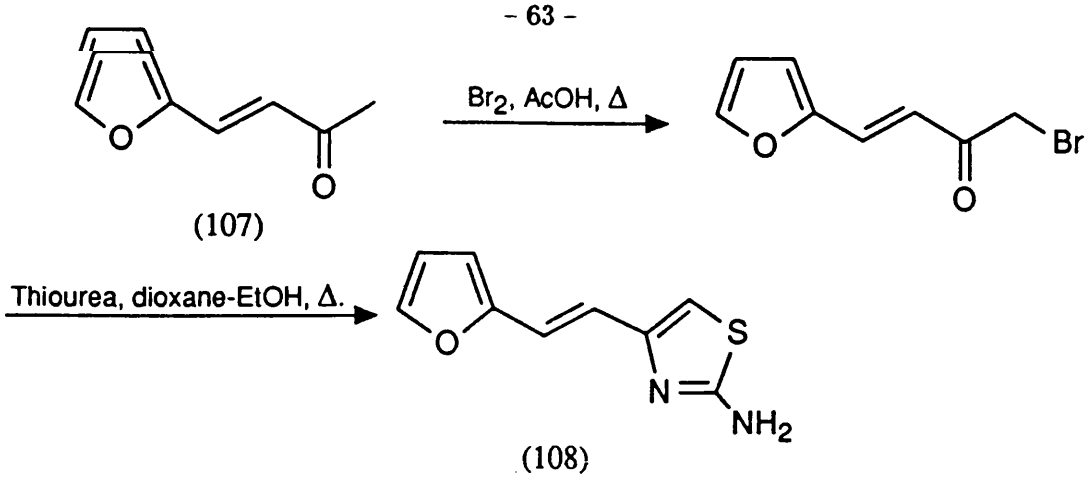


(106) (41)

Scheme 4.13.

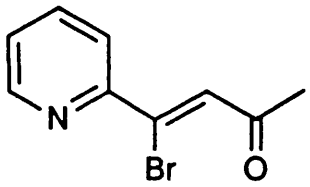
Russian workers have reported the specific α-bromination of 4-(2-furanyl)enones[18] (107, scheme 4.14). This method employed bromine in acetic acid at reflux temperature to achieve the required transformation. The bromomethylenones were then treated with thiourea to afford the corresponding 2-thiazolamines (108).

When we subjected the 2-pyridylenone (105) to these conditions a product was isolated which decomposed fairly rapidly at room temperature. This compound was tentatively assigned the structure (109, fig. 4.1) based on the ^{1}H n.m.r. and mass



Scheme 4.14.

spectral data.[19, 20] The most significant peak in the ^1H n.m.r. spectrum is a 3-proton singlet at δ_H 2.1 corresponding to the resonance of the methyl protons, confirming that bromination had not occurred at this position.

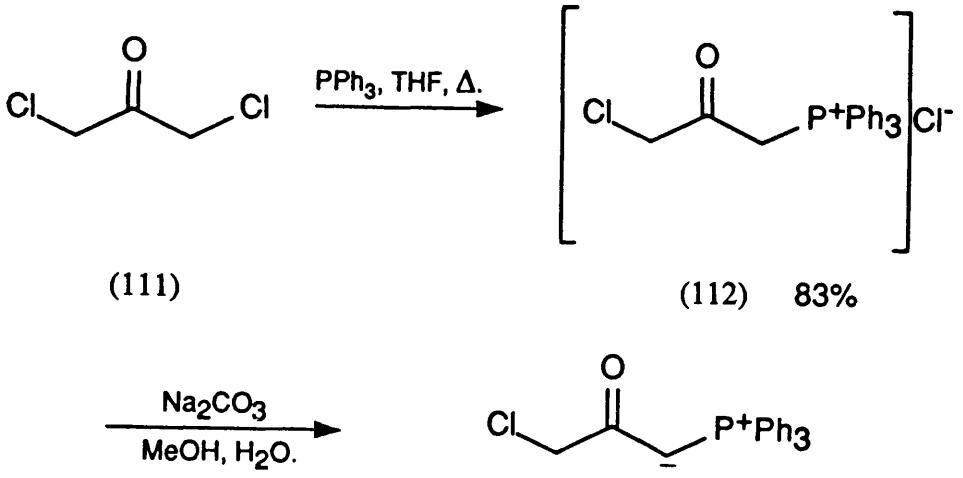


(109)

Fig. 4.1.

We then decided that the most efficient way of preparing the required halomethylenone (106) would be directly from 2-pyridinecarboxaldehyde and the ylid (110). This compound is known [21] and it was prepared according to the literature procedure from 1,3-dichloroacetone (111) and triphenylphosphine to afford the salt (112) which was then converted to the ylid (110) with sodium carbonate in high overall yield (scheme 4.15).

Hudson and Chopard have reacted the ylid (110) with several aldehydes to afford the corresponding enones[21] but the 2-pyridylchloromethylenone (113) has not been reported to have been synthesised by this or any other route. We found that stirring the ylid (110) and 2-pyridinecarboxaldehyde in dichloromethane overnight

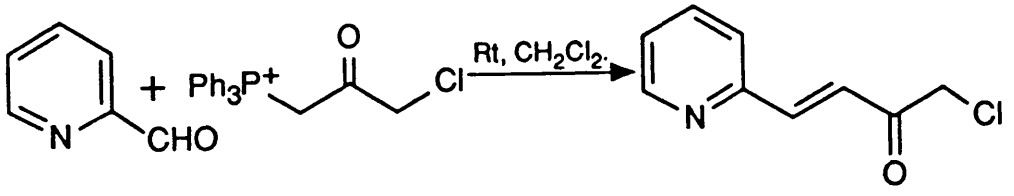


(111) (112) 83%

(110) 98%

Scheme 4.15.

at room temperature gave the required product in reasonable yield (scheme 4.16). Purification of the chloromethylenone (113) was complicated by the presence of triphenylphosphine oxide in the reaction mixture, which is notoriously difficult to remove by chromatography. However, we found that once the solvents were removed from the reaction mixture the residue could be extracted with hot ethyl acetate. On cooling the combined extracts, triphenylphosphine oxide crystallised out, and the mother liquors containing the required product could then be concentrated and the residue chromatographed. This procedure was found to be successful on a multigram scale.

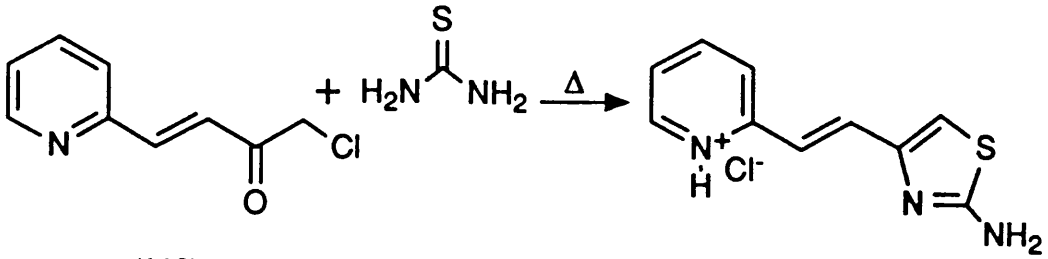


(106) (110) (113) 67%

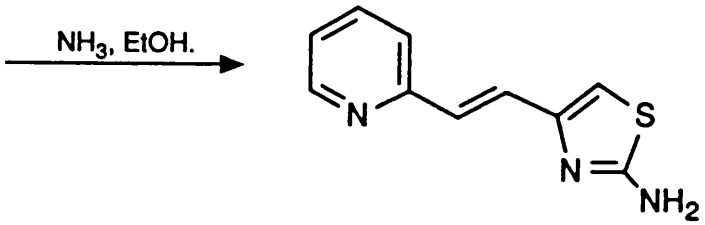
Scheme 4.16.

Once again it was the n.m.r. spectral data of the product from this reaction

which confirmed that the compound isolated was the chloromethylenone (113). For example, the 2-proton singlet at δ_H 4.35 in the ^1H n.m.r. spectrum clearly corresponds to the chloromethyl proton resonances. Also, the coupling constant for the spin-spin system of the alkene protons (resonating at δ_H 7.43 and δ_H 7.70) is 16 Hz, indicating a *transoid* relationship for the protons. In the ^{13}C n.m.r. spectrum, 1-C resonates as a triplet at δ_C 47.7, which is a further piece of evidence supporting our assignment.



(113) (114) 99%



(41) 95%

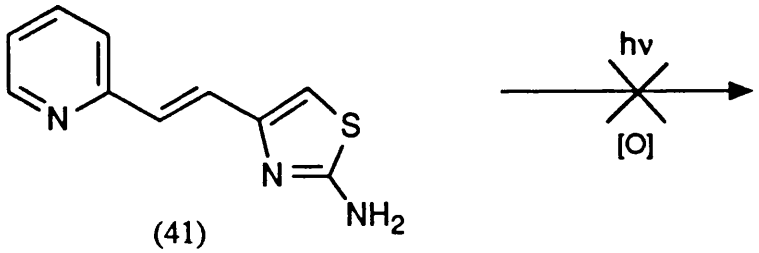
Scheme 4.17.

The ethenylthiazolamine hydrochloride (114) was prepared from the chloromethylenone (113) and thiourea by heating the mixture under gentle reflux in *p*-dioxane-ethanol (scheme 4.17), the method of thiazole formation used by Saldabols.[18] The solid compound crystallised from the cold reaction mixture in good yield (99%), and could then either be recrystallised from ethanol or converted to the free base (41) by stirring with 10% ethanolic ammonia.[17] That the 2-thiazolamine hydrochloride (114) had formed in the reaction was clearly indicated by the ^1H n.m.r. spectrum of the compound. It is interesting to compare the chemical shifts of the pyridyl proton resonances of the chloromethylenone (113), the 2-thiazolamine

hydrochloride (114) and the ethenylthiazolamine (41) (see table 4.1). There is a clear downfield shift in the proton resonances of the ethenylthiazolamine hydrochloride (114) compared with the pyridyl proton resonances of the free base (the assignments were based on literature data[20]). The u.v. spectra of (114) and (41) were recorded and the data are tabulated in the appendices. Also displayed are the u.v. spectral data for the isoxazoles (45), (76) and (89), as well as other related heterocyclic stilbene analogues, and *trans* stilbene (90).

^{1}H n.m.r. Spectral Data for (113), (114) and (41). (Pyridyl proton resonances only).				
Cpd.	6'	5'	4'	3'
(113)	8.68	7.32	7.76	7.48
Cpd.	6"	5"	4"	3"
(114)	8.66	7.62	8.23	8.02
(41)	8.53	7.21	7.74	7.47

· *Table 4.1*



(41)

Scheme 4.18.

Both the hydrochloride (114) and the free amine (41) were subjected to Cava's photocyclisation conditions. This unfortunately led to the degradation of the starting thiazoles, and attempted purification of the reaction mixture yielded only decomposition material. In a final attempt to get the reaction to succeed, we used a different

set of mild conditions [22] which employed ethanol as the solvent and air as the oxidant. However, we found that no products could be obtained from the reaction mixture. Thiazoles are known to rearrange in a similar manner to oxazoles and isoxazoles under certain photochemical conditions, and it seems likely that this may have contributed to the degradation of the molecule. [23]

It was at this point that we decided to concentrate on alternative methods of modification of our molecular system.

References.

1. A. Smakula, *Z. Phys. Chem.*, 1934, **B25**, 90.
2. C. O. Parker and P. E. Spoerri, *Nature*, 1950, **166**, 603.
3. E. V. Blackburn and C. J. Timmons, *Quart. Rev.*, 1969, **23**, 482.
4. F. B. Mallory and C. W. Mallory, *Org. React. (N.Y.)*, 1984, **30**, 1.
5. J. B. Hendrickson and J. G. de Vries, *J. Org. Chem.*, 1984, **50**, 1688.
6. S. O. de Silva and V. Snieckus, *Synthesis*, 1971, 254.
7. S. O. de Silva and V. Snieckus, *Can. J. Chem.*, 1974, **52**, 1294.
8. G. Cooper and W. J. Irwin, *J. Chem. Soc., Perkin Trans. 1*, 1976, 75.
9. G. Lindgren, K-E. Stensio, and K. Wahlberg, *J. Heterocycl. Chem.*, 1980, **17**, 679.
10. J. L. Cooper and H. H. Wasserman, *J. Chem. Soc., Chem. Commun.*, 1969, 200.
11. V. H. Rawal, R. J. Jones, and M. P. Cava, *Tetrahedron Lett.*, 1985, **26**, 2423.
12. V. H. Rawal, R. J. Jones, and M. P. Cava, *J. Org. Chem.*, 1987, **52**, 19.
13. F. Benington, R. D. Morin, and M. A. Khaled, *Synthesis*, 1984, 619.

14. L. C. King and R. J. Hlavacek, *J. Am. Chem. Soc.*, 1950, **72**, 3722.

15. L. C. King and I. Ryden, *J. Am. Chem. Soc.*, 1947, **69**, 1813.

16. L. C. King and R. M. Dodson, *J. Am. Chem. Soc.*, 1945, **67**, 2242.

17. S. Schulman, *J. Org. Chem.*, 1949, **14**, 382.

18. N. Saldabols and V. V. Krylova, *Khim. Geterotsikl. Soedin.*, 1969, 555. CA 72:21633.

19. D. W. Brown, A. J. Floyd, and M. Sainsbury, *Organic Spectroscopy,* Wiley (1988).

20. E. Pretsch, T. Clerc, J. Seibl, and W. Simon, *Tables of Spectral Data for Structure Determination of Organic Compounds,* Springer , Berlin, English ed. (1983).

21. R. F. Hudson and P. A. Chopard, *J. Org. Chem.*, 1963, **28**, 2446.

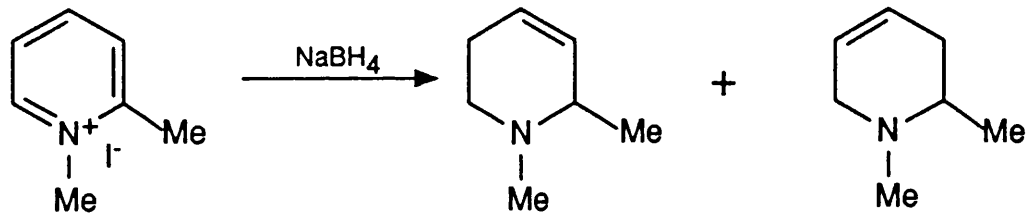
22. S. F. Dyke and M. Sainsbury, *Tetrahedron*, 1967, **23**, 3161.

23. I. Saito, T. Morrii, Y. Okumura, S. Mori, K. Yamaguchi, and T. Matsuura, *Tetrahedron Lett.*, 1986, **27**, 6385.

5. The Reduction of 2-Alkylpyridines.

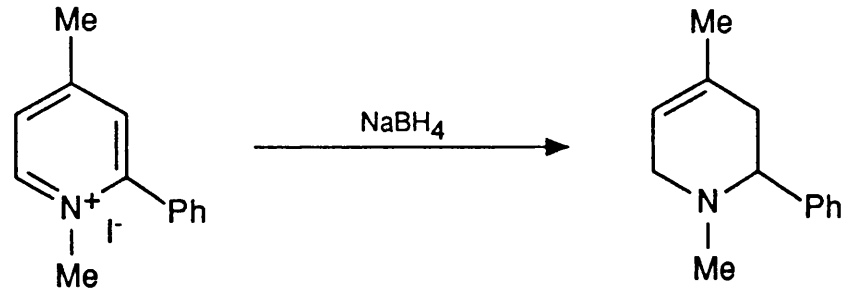
The reduction of pyridines and their quaternary salts to the corresponding dihydro, tetrahydro, and hexahydro derivatives has been the subject of a number of reviews.[1-4] However, there is a dearth of information regarding the reduction of 2-substituted pyridines. We were particularly interested in the reduction of such compounds leading to the formation of their 1,2,5,6-tetrahydro derivatives.

In the literature there are two relevant studies carried out in the 1960's. In the first of these, Ferles reduced 2-picoline methiodide with sodium borohydride to yield the tetrahydropyridines (115) and (116) in a ratio of ≈ 1:6 (scheme 5.1).[5] The second study, carried out by Lyle, involves the reduction of 1,4-dimethyl-2-phenylpyridinium iodide (117) again with sodium borohydride to afford the tetrahydropyridine (118) as the sole product (scheme 5.2).[6]



(115) (116)

Scheme 5.1.

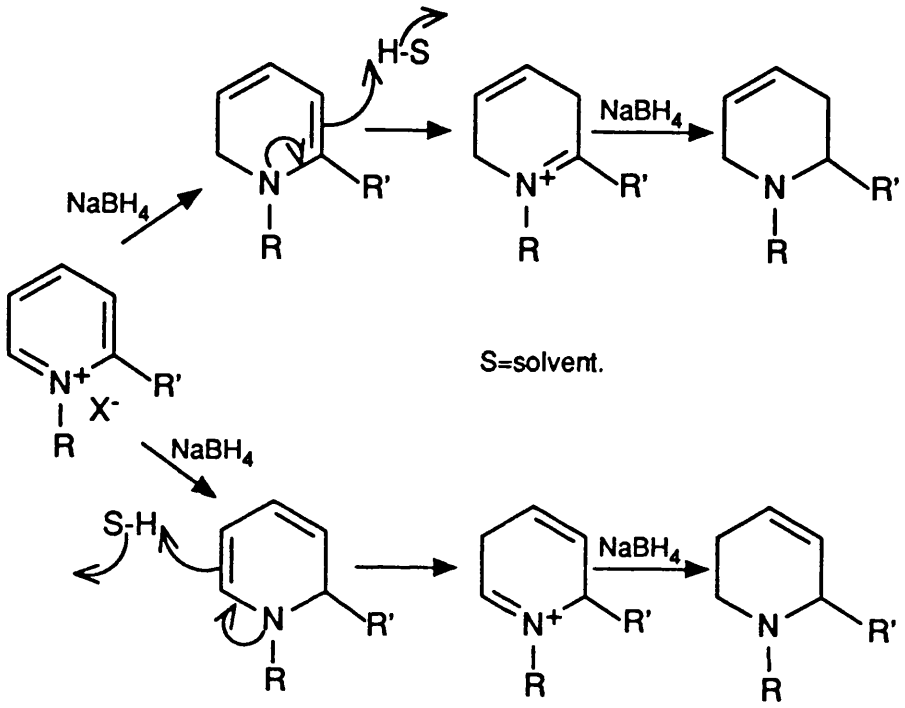


(117) (118)

Scheme 5.2.

The mechanism of these reactions is outlined in scheme 5.3. The initial hydride

ion attack occurs at either position 2 or position 6 of the ring; the intermediate enamine then abstracts a proton from the solvent and the resultant iminium species is reduced by a second hydride ion to form the corresponding tetrahydropyridine. Thus, it is the *initial* position of hydride ion attack which ultimately determines the position of the double bond in the product. The examples cited above illustrate that the substituent at position 2 exerts a considerable influence over this initial step in the reduction, and that its stereochemical and electronic characteristics are likely to determine where the unsaturation will occur in the product.

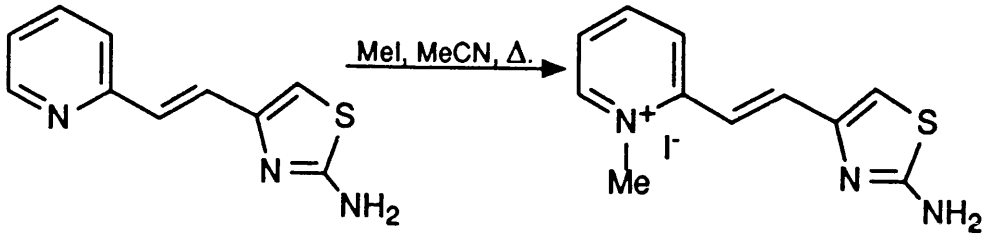


Scheme 5.3.

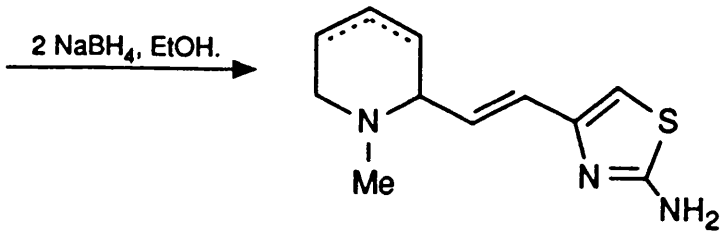
With this in mind, we were keen to investigate the reduction of our pyridyl compounds. This first required the preparation of the corresponding quaternary salts.

The ethenylthiazolamine (41) was quaternised by reaction with iodomethane in hot acetonitrile (scheme 5.4). We discovered that it was difficult to force this reaction to go to completion, and that a quantity of starting material was usually recovered, which could either be recycled or carried over with the product to be

removed after the next stage. The quaternary salt isolated in this reaction was identified from its spectral data as the *N*-methylpyridinium iodide (119, scheme 5.4). No product resulting from the quaternisation of the thiazolamine portion of the molecule was identified in the reaction mixture.



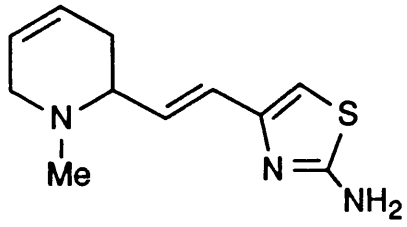
(41) (119) 69%



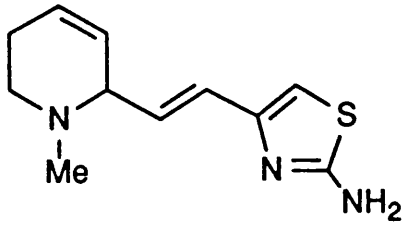
(120, 121) 55%

Scheme 5.4.

The *N* methylpyridinium iodide (119) was treated with 2 equivalents of sodium borohydride in ethanol at 0°C (scheme 5.4). Ethanol was found to be the ideal protic solvent for this reaction, since unlike methanol it does not readily decompose sodium borohydride. Two new compounds were isolated from the reaction mixture, and the structures assigned from their n.m.r. spectra.



(120)



(121)

Fig. 5.1.

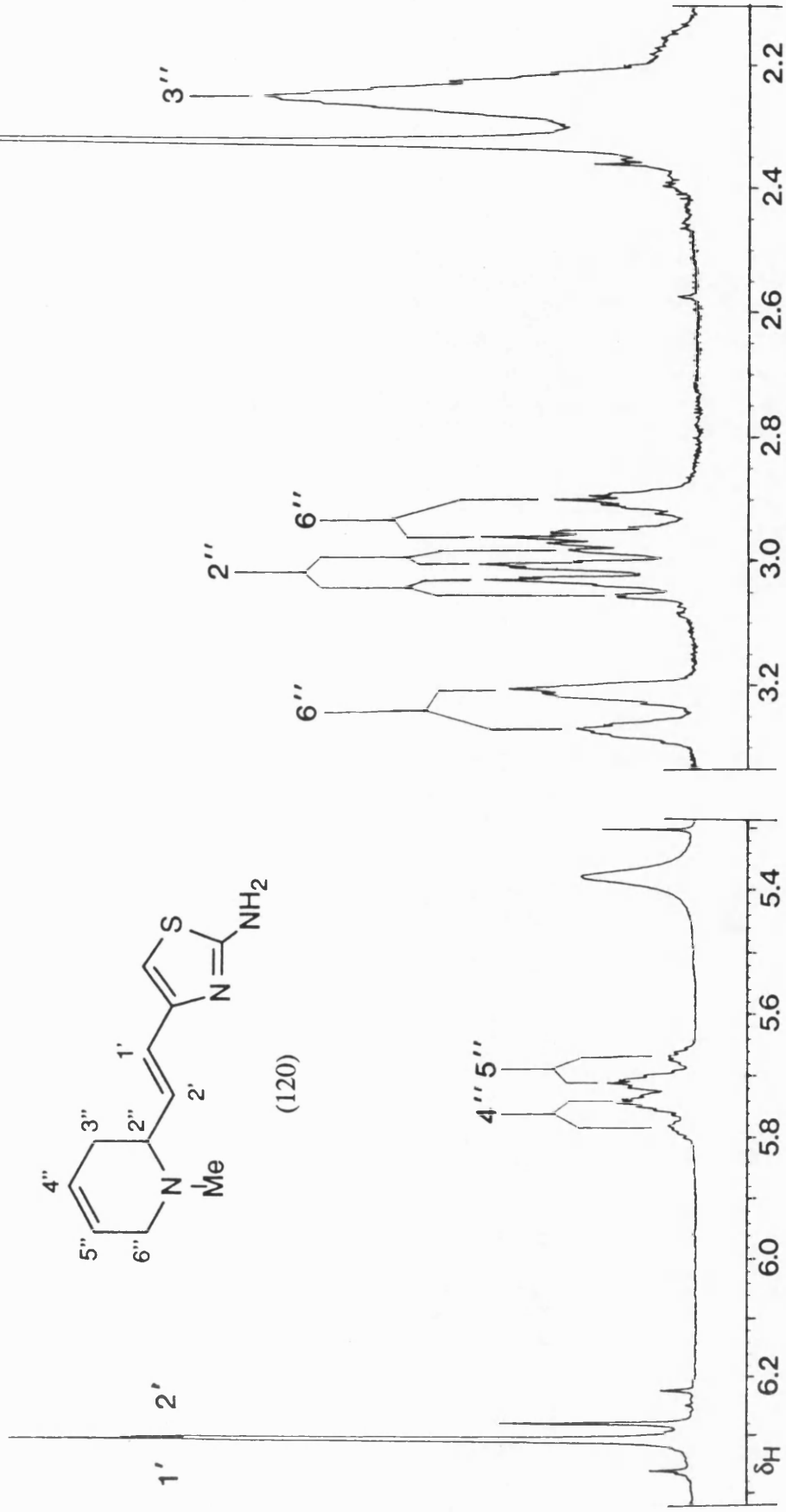
The first product was isolated as a solid in good yield (55%). The molecular ion in the mass spectrum of this compound appears at m/z 221, corresponding to the mass expected for the isomeric tetrahydropyridines (120 and 121, fig. 5.1). The ^1H n.m.r. spectrum of the compound exhibits two groups of signals resulting from the resonances of vinylic protons. One set of peaks due to two proton resonances appears as a simple pair of doublets at $\approx \delta_H$ 6.3 (J 16 Hz, indicating a *transoid* relationship). Clearly, these peaks are due to the resonances of the side chain vinylic protons (1'-H and 2'-H) of the tetrahydropyridine. Slightly upfield from these resonances are a symmetrical pair of doublets with complex hyperfine splitting (δ_H 5.69 and δ_H 5.77). The coupling constant between the peaks (J 12 Hz) indicates that the protons responsible for these resonances possess a *cisoid* relationship, and hence are sited in the tetrahydropyridine ring.

The most significant feature of the ^1H n.m.r. spectrum is the symmetrical nature of the peaks at δ_H 5.69 and δ_H 5.77 (fig. 5.2) due to the ring vinylic proton resonances. This implies that the protons reside in very similar magnetic environments *i.e.* that the protons adjacent to each of the vinylic protons have very similar characteristics. A comparison of the two structures (120 and 121, fig. 5.1) indicates that in the tetrahydropyridine (120) 4''-H and 5''-H are each adjacent to methylene protons at positions 3'' and 6'' respectively. This is in direct contrast to the situation in the tetrahydropyridine (121) in which the vinylic proton 3''-H is adjacent to the methine proton at position 2'', whilst 4''-H is next to methylene protons at position 5''. Thus, the ^1H n.m.r. spectral data exhibited by the compound more closely fits the structure (120), since the tetrahydropyridine (121) would be expected to give rise to a more complex, asymmetric set of signals in the vinylic region of the ^1H n.m.r. spectrum.

Operating on the assumption that the structure of our compound was the tetrahydropyridine (120), we were able to assign the rest of the peaks in the ^1H

Fig. 5.2.

^{1}H n.m.r. spectrum of (120).



(120)

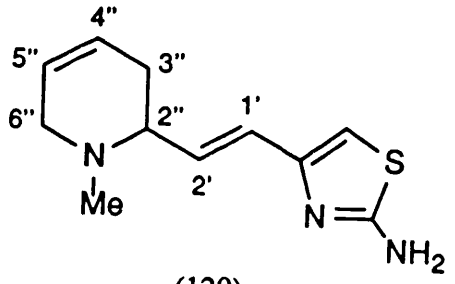
n.m.r. spectrum by comparison with literature data [6,7] and by using decoupling difference (subtractive decoupling) ^1H n.m.r. spectroscopy. In this technique, the normal ^1H n.m.r. spectrum is subtracted from the decoupled spectrum, allowing the unambiguous assignment of coupled resonances. The nett effect of subtractive decoupling is an enhancement of the proton resonances coupled to the proton being irradiated, whereas the signals due to protons not coupled to the irradiated proton tend to zero. (The peak due to the resonance of the irradiated proton itself inverts.)

The results of the decoupling difference experiment are presented in table 5.1. From literature assignments it was clear that the peak at δ_H 2.25 is due to the resonances of 3"-H_2, whilst the signals at δ_H 2.94, δ_H 3.02 and δ_H 3.25 correspond to the resonances of the protons at positions 2" and 6". Decoupling the resonance at δ_H 3.25 produces enhancements at δ_H 2.94, δ_H 5.69 and δ_H 5.77 (the latter pair being the signals due to the tetrahydropyridine ring vinylic protons), indicating coupling between these resonances. There is a diminution however of the signals at δ_H 2.25 (3"-H) and $\approx \delta_H$ 6.3 (the signal due to the resonances of the side chain vinylic protons) implying zero coupling between these resonances and the irradiated resonance. Similarly, decoupling at δ_H 2.94 causes enhancements at δ_H 3.25 and δ_H 5.7. Thus, the doubled multiplets at δ_H 2.94 and δ_H 3.25 (J 17 Hz) are due to the resonances of the geminal pair at position 6". Irradiation at δ_H 3.02 on the other hand leads to an enhancement of the resonances at $\approx \delta_H$ 6.3, whereas the signals at δ_H 5.69 and δ_H 5.77 collapse almost to zero. This result would be expected if the irradiated signal is due to the methine proton at position 2", thus confirming our structural allocation.

The mechanism of formation of the tetrahydropyridine (120) is illustrated in scheme 5.5. Initial hydride ion attack occurs at position 6" and the intermediate enamine abstracts a proton from the solvent to form an iminium species. This is then reduced by a second equivalent of hydride ion, leaving the ring vinylic unit between positions 4" and 5" as in structure (120). Our result is therefore in agreement with

Decoupling Difference Spectral Data for (120).			
Decoupled resonance (δ_H).	Enhance-ment (δ_H).	Zero enhance-ment (δ_H).	Assign-ment.
3.25	2.94, 5.69, 5.77	2.25, ≈ 6.3	6"-H_1
3.02	≈ 6.3	5.69, 5.77	2"-H
2.94	3.25, 5.69, 5.77	---	6"-H_1

Table 5.1.

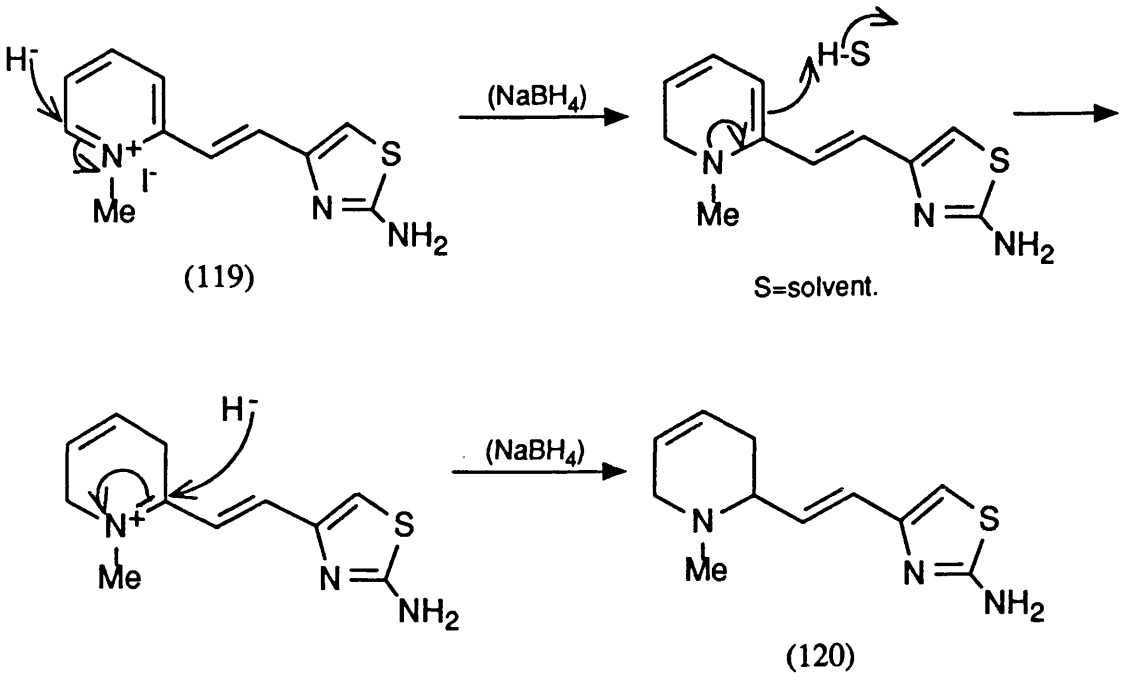


(120)

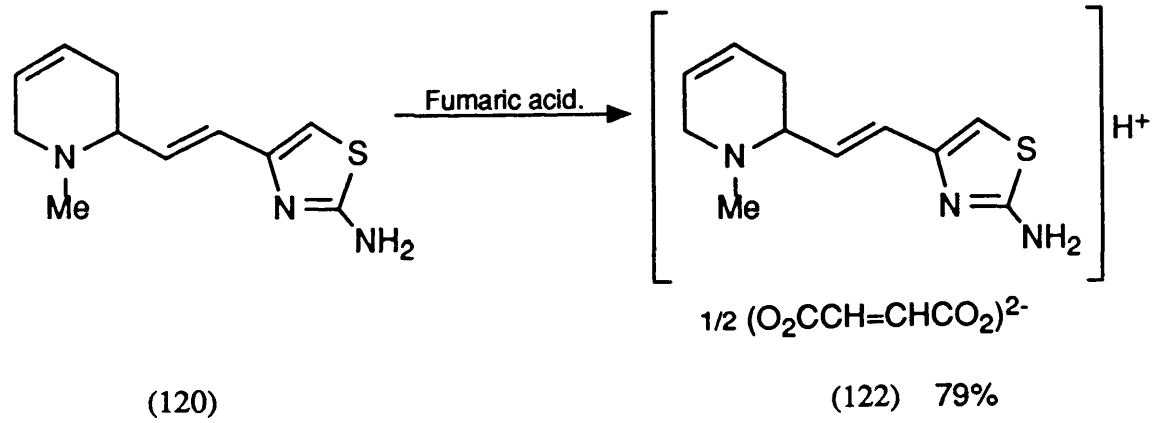
Lyle's study of the reduction of 1,4-dimethyl-2-phenylpyridinium iodide (117, scheme 5.2).

The ethenyltetrahydropyridine (120) was converted to its fumarate salt (122, scheme 5.6) and 0.5 g of this compound was submitted for biological testing (see appendix 1).

The second product isolated in the reduction of the *N*-methylpyridinium iodide (119) is an oil of lower R_F than the ethenyltetrahydropyridine (120), and it possesses interesting physical characteristics. The compound was not only found to be soluble

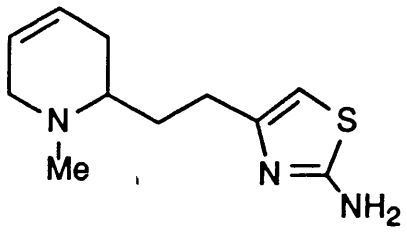


Scheme 5.5.



Scheme 5.6.

in organic solvents such as dichloromethane, but was also highly soluble in aqueous media. When we repeated the reaction we found that we were able to increase the yields of both the products by altering the work-up procedure, thus avoiding the loss of the water-soluble oil in aqueous washes. This was achieved by removing the water used in the work up azeotropically with 2-propanol to afford a residue which could be chromatographed, rather than extracting the aqueous phase with ethyl acetate. This compound has M^+ 223, which indicates that it is an homologue of the ethenyl-tetrahydropyridine (120).

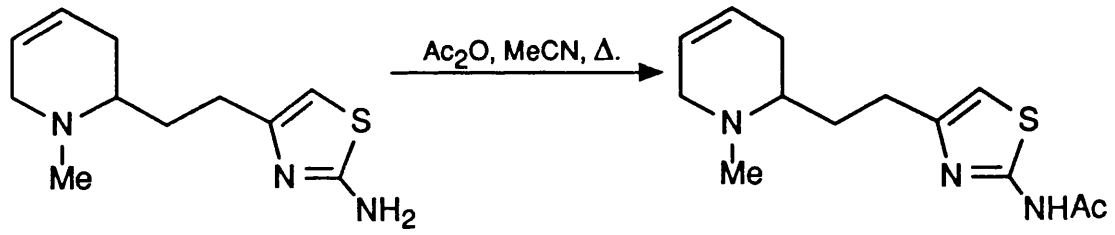


(123)

Fig. 5.3.

In the ^{1}H n.m.r. spectrum there are no peaks in the region of δ_H 6.3 (apart from a singlet at δ_H 6.10 corresponding to the thiazole 5–H resonance). However, a symmetrical pair of doubled multiplets are present at δ_H 5.63 and δ_H 5.73 (J 11Hz). The latter peaks clearly correspond to the tetrahydropyridine ring 4"–H and 5"–H resonances of structure (123, fig. 5.3).

Based on data from the literature [7] and those for the ethenyltetrahydropyridine (120), it was now possible for us to assign the other peaks in the ^{1} H n.m.r. spectrum. Thus doubled multiplets at δ_H 3.00 and δ_H 3.16 (J 17 Hz) are due to the 6" -H_2 resonances, whilst a multiplet centred at δ_H 2.55 corresponds to the resonances of the protons at positions 1' and 2". Corroboration of these conclusions was obtained from the COSY n.m.r. spectrum (fig. 5.4, table 5.2) of the amide derivative (124), formed by N acetylation with acetic anhydride (scheme 5.7).



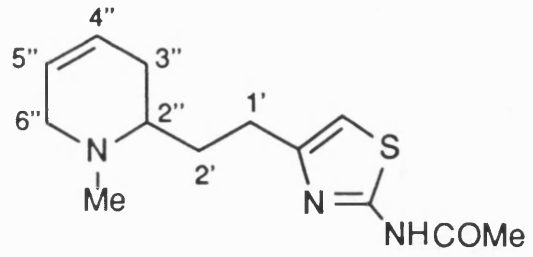
(123) (124) 90%

Scheme 5.7.

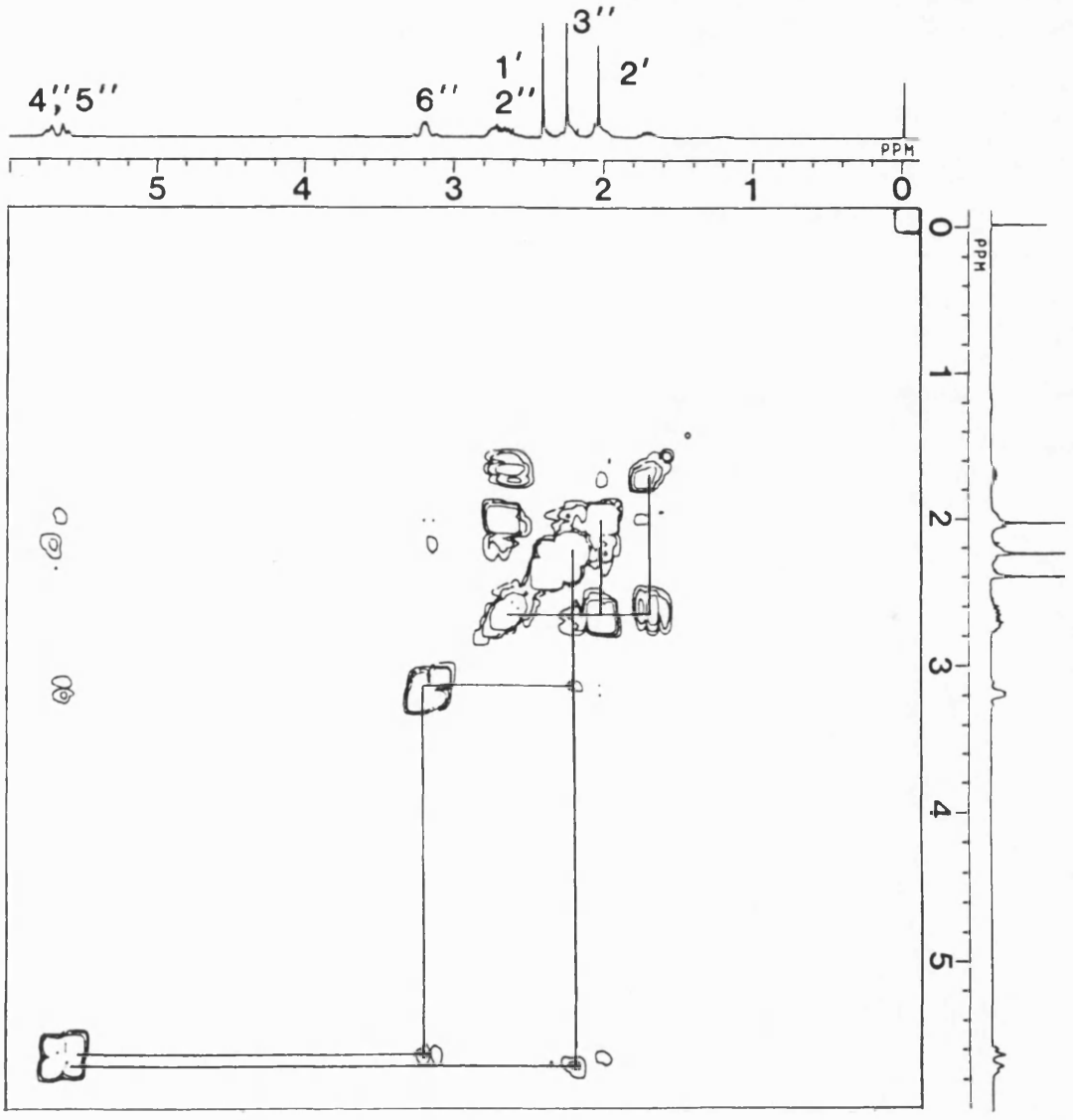
Thus, cross peaks from the vinylic proton resonances at δ_H 5.63 and δ_H 5.76 indicate coupling with the peaks due to 6"–H_2 (δ_H 3.17, δ_H 3.28) and 3"–H_2 (δ_H 2.05, δ_H 2.25). Crucially, there are no cross peaks from the vinylic resonances to a multi-

Fig. 5.4.

COSY spectrum of (124). (Showing cross peaks).



(124)



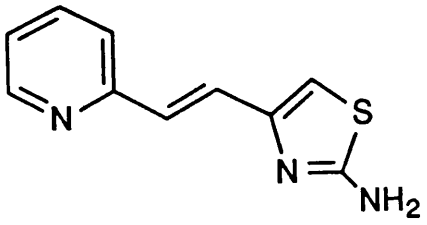
plet at δ_H 2.70 which corresponds to the signals of the protons[7] at positions 1' and 2". The multiplet at δ_H 2.70 does, however, exhibit coupling with peaks at δ_H 1.70, δ_H 2.05 and δ_H 2.25, clearly indicating that these last signals are due to the resonances of 2'-H_2 and 3"-H_2. Hence, a full assignment is possible.

COSY Spectral Data for (124).	
Observed δ_H. (Assignment.)	Cross Peaks (δ_H). (Assignment.)
5.76, 5.63 (4"-H), (5"-H)	3.28, 3.17, 2.25, 2.05 (6"-H), (6"-H), (3"-H), (3"-H)
2.70 (1'-H_2, 2"-H)	2.25, 2.05, 1.70 (3"-H), (3"-H, 2'-H), (2'-H)

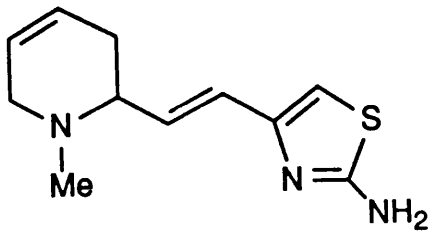
Table 5.2.

These results led us to consider whether the reduction of the quaternary salt of an ethylpyridine *e.g.* (125, fig. 5.5) would lead to the isolation of a set of reaction products which are different from those isolated after the reduction of the vinyl analogue (41). We also sought a more efficient way of preparing the ethyltetrahydropyridine (123) than merely isolating the compound as a side product in the reduction of the *N*-methylpyridinium iodide (119). With these aims in mind we embarked on a study of methods of reduction of the ethenylthiazolamine (41) and the ethenyltetrahydropyridine (120).

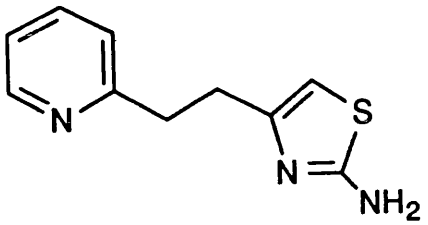
Turning our attention firstly to the ethenylthiazolamine (41) we found that the compound is resistant to catalytic hydrogenation with heterogeneous catalysts such as Pd/C, Raney Ni and PtO_2. This is in stark contrast to the ease with which we were able to hydrogenate the isoxazole analogue (45, fig. 5.5), and we suspect that the sulphur atom in the thiazole moiety acts as a catalyst poison. It was clear there-



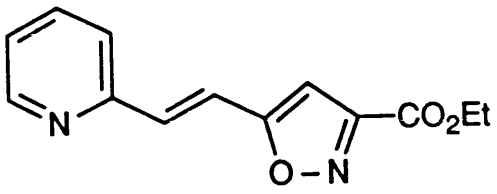
(41)



(120)



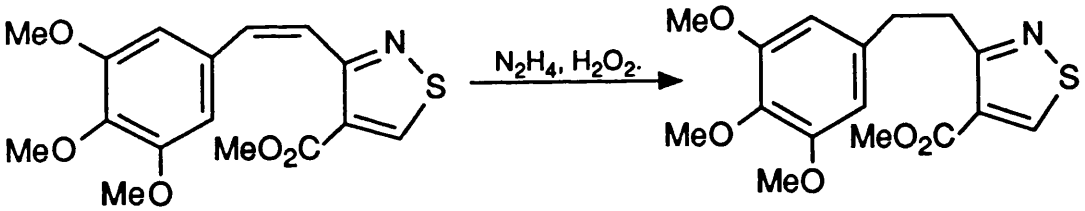
(125)



(45)

Fig. 5.5.

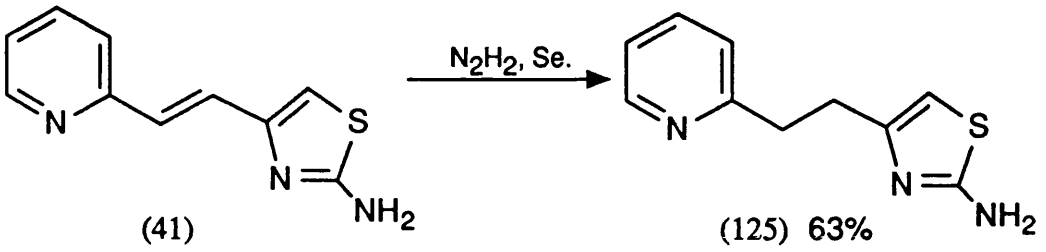
fore that we required an alternative method of hydrogenation.



Scheme 5.8.

In order to reduce the double bond in an intermediate containing an isothiazole moiety, di-imide has been used to good effect[8] (scheme 5.8). Di-imide is a highly active species which may be generated *in situ* by a variety of methods.[9,10] One such procedure is based on the oxidation of hydrazine. Japanese workers have developed a method employing selenium as the oxidant, the selenium being catalytic with respect to di-imide generation if the reaction is carried out in air.[11] We found that this method was effective in hydrogenating the ethenylthiazolamine (41) to the ethylthiazolamine (125, scheme 5.9) in 63% yield (based on recovered starting material). The reaction was clean with no side products, although the conversion was always incomplete, despite the fact that an excess of reagents were used.

Unfortunately, since starting material and product have similar R_F values, chromatographic separation is difficult.

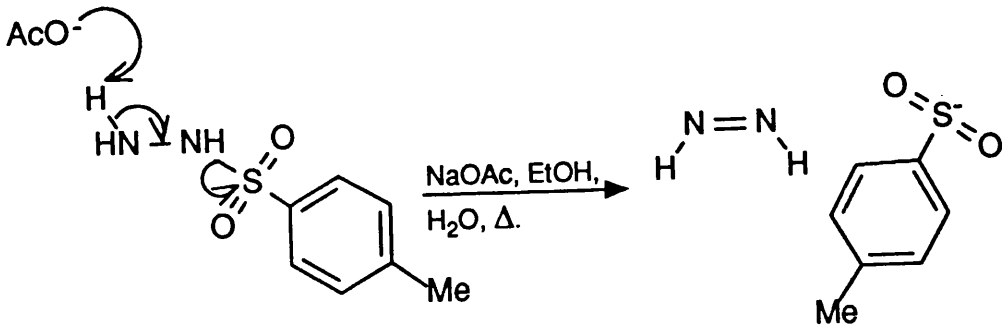


Scheme 5.9.

Sodium periodate has also been used to oxidise hydrazine to di-imide. The procedure we followed was that described by Schlessinger.[12] However, when applied to the ethenylthiazolamine (41) this technique led only to the recovery of starting materials.

At this point we turned away from oxidative methods of di-imide generation and instead attempted a procedure employed by Hart.[13] This involves the sodium acetate induced elimination of *p*-toluenesulphinic acid from *p*-toluenesulphonhydrazide (scheme 5.10). Typically, the di-imide was generated gradually by slowly dripping a dilute aqueous solution of sodium acetate into a solution of the substrate (41) and *p*-toluenesulphonhydrazide in boiling ethanol. We observed that the ethylthiazolamine (125) was produced *via* this reaction but only in 19% yield, with no starting material remaining after work-up. This, together with the fact that dilute solutions are required for this reaction would have caused problems if the procedure had been attempted on a multigram scale.

Our attention was next directed to the reduction of the ethenyltetrahydropyridine (120, fig. 5.5). A particular point of interest was to discover which of the double bonds in this compound would be reduced when it was subjected to hydrogenation conditions. Unfortunately we were unable to effect hydrogenation over Raney nickel catalyst, and di-imide reductions with selenium/hydrazine, hydrogen peroxide/hydrazine and potassium azodicarboxylate (PADA)[14-16] were also



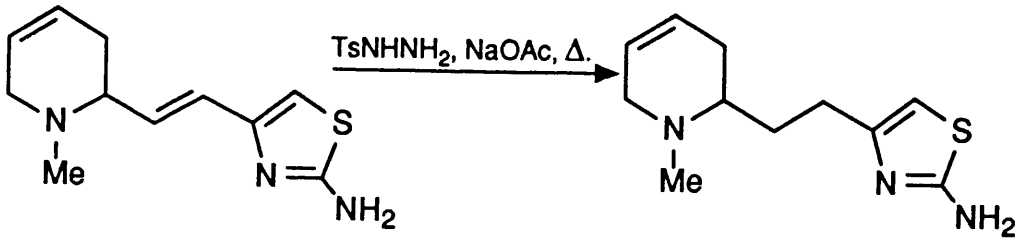
Scheme 5.10.

unsuccessful.

A reaction with sodium acetate/*p*-toluenesulphonhydrazide converted the substrate to a compound with spectral data identical to those of the ethyltetrahydropyridine (123) in 39% yield (scheme 5.11) [no product corresponding to the piperidine (126, fig. 5.6) was isolated]. The water-soluble nature of the ethyltetrahydropyridine (123) hindered our efforts to increase the yield of the product, and we therefore attempted a related procedure developed by Reese.[17] This method employs 2,4,6-trimethylbenzenesulphonyl hydrazide (127, fig. 5.7) which eliminates the corresponding sulphinic acid on heating in boiling methanol, thereby avoiding the need for aqueous base. Using a large excess of 2,4,6-trimethylbenzenesulphonyl hydrazide (127) in the presence of the ethenyltetrahydropyridine (120) a partial conversion of the substrate to the ethyltetrahydropyridine (123) was effected. Once again it was difficult to separate the product from the starting material using column chromatography.

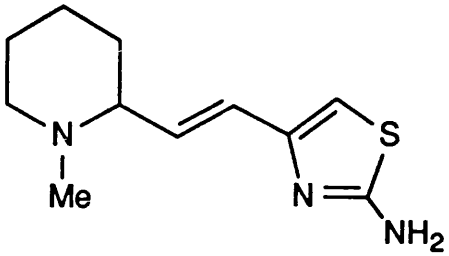
Sodium hydrotelluride was originally developed as a reagent by Barton[18] and has since been used by other groups of workers to reduce α,β-unsaturated carbonyl compounds[19] and 3-ethenylquinolines. [20] The reducing agent is generated *in situ* from tellurium powder and sodium borohydride in the presence of ethanol at room temperature according to the equation in scheme 5.12.

Reaction of the ethenylthiazolamine (41) with sodium hydrotelluride gave the



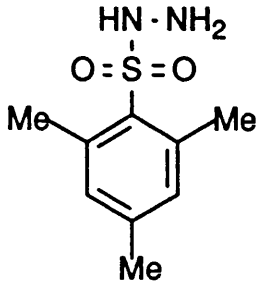
(120) (123) 39%

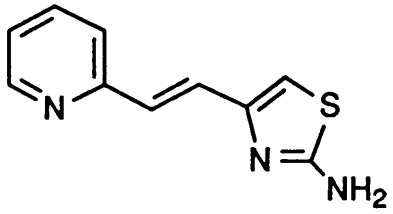
Scheme 5.11.



(126)

Fig. 5.6.





(127) (41)

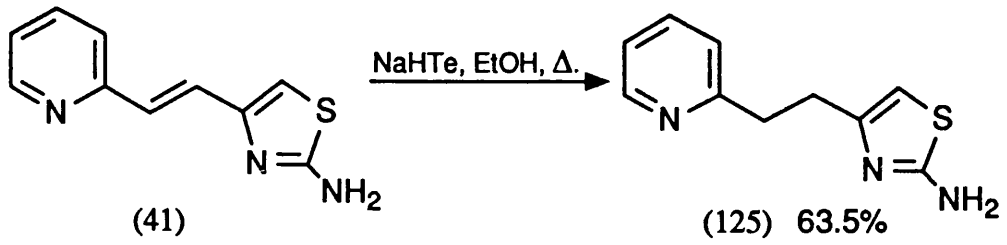
Fig. 5.7.

$$Te + NaBH_4 + 3\ EtOH \longrightarrow B(OEt_3) + 3\ H_2 + NaHTe$$

Scheme 5.12.

reduced product (125, scheme 5.13) in 63.5% yield and by generating an excess of the telluride reagent a complete conversion of starting material could be accomplished. After an initial induction period a highly exothermic reaction commenced. When this had subsided, the mixture was heated under reflux. Some workers have performed similar reactions under an argon atmosphere, but we found that nitrogen was perfectly adequate. Work-up and purification was effected by filtration of the mixture

to remove the tellurium (which may be recycled), followed by chromatography or crystallisation. On a large scale (≈ 50 g starting material) the reaction has a tendency to overheat and reflux violently.

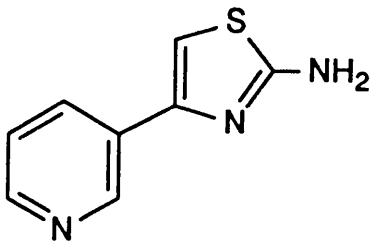


Scheme 5.13.

In a final attempt to discover a more efficient reducing agent for the ethenyltetrahydropyridine (120), we attempted the hydrogenation of the compound in the presence of tris(triphenylphosphine)rhodium(I) chloride (Wilkinson's catalyst). This homogeneous catalyst is known in some cases to effect reduction of carbon–carbon double bonds in the presence of sulphur.[21] Stirring the ethenyltetrahydropyridine (120) under hydrogen (4 atmospheres) with this reagent at 60°C resulted only in the recovery of starting material containing base line decomposition products.

With a supply of the ethylthiazolamine (125) to hand, its further reduction was investigated. Firstly, however, a suitable protecting group for the thiazole primary amino function was required, since the 2-thiazolamine moiety is not deactivated by conjugation as it is in the ethenylthiazolamine (41, fig. 5.7). In the latter compound, the inductive effect of the pyridine is transmitted through the connecting double bond, preventing quaternisation at either of the thiazole nitrogens (see page 70). Interestingly, other workers have found that treatment of the 4-(3-pyridyl)-2-thiazolamine (128, fig. 5.8) with iodomethane leads to quaternisation at the pyridyl nitrogen atom only.[22]

We thus required a protecting group for the ethylthiazolamine (125) that would be stable to the conditions of *N*-quaternisation and sodium borohydride reduction. Meakins and coworkers have studied the use of *N*-substituted 2,5-dimethylpyrroles as masking agents for primary amines.[23] This protecting group is reported to be

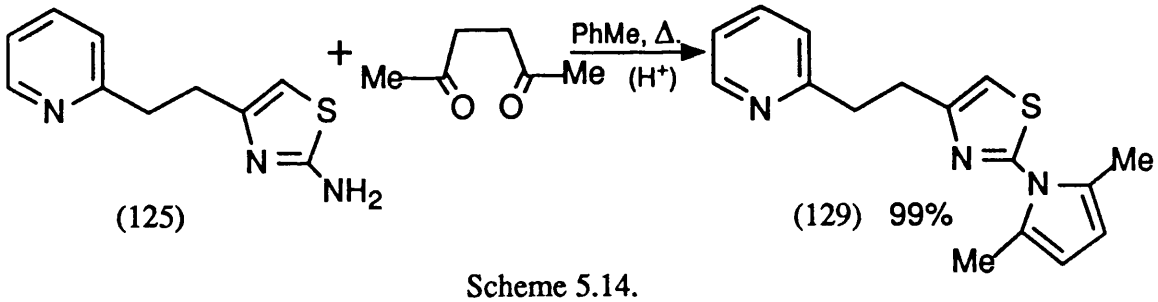


(128)

Fig. 5.8.

stable under a range of conditions, whereas deprotection is effected by treatment with hydroxylamine hydrochloride.

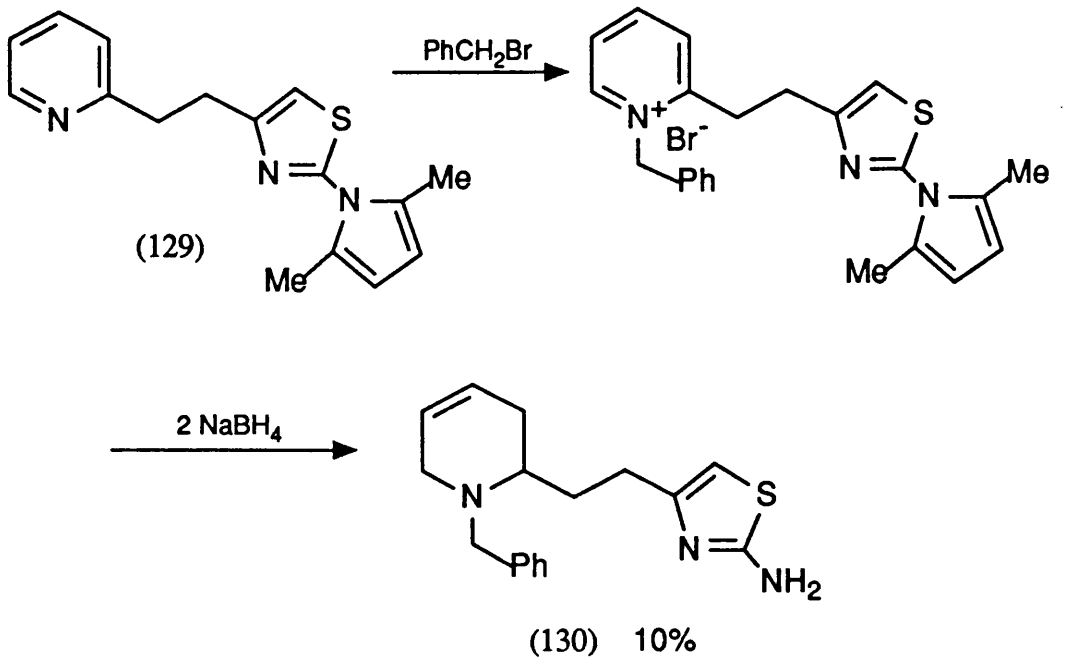
The protection of the amino function in our compound was accomplished by heating the ethylthiazolamine (125) with acetonylacetone under reflux in the presence of a catalytic quantity of *p*-toluenesulphonic acid (scheme 5.14). The resulting 2,5-dimethylpyrrole (129) was isolated as an oil (99%) and fully characterised. It is interesting to note that in the ^1H n.m.r. spectrum of the compound the resonances of 1'-H_2 and 2'-H_2 form a singlet at δ_H 3.20.



Scheme 5.14.

This compound was quaternised with benzyl bromide rather than iodomethane, since we considered that dealkylation of the resultant *N*-benzyl derivative might be accomplished with greater ease at a later stage in the synthetic sequence than the *N*-methyl compound. Treatment of the 2,5-dimethylpyrrole (129) with benzyl bromide in acetonitrile under reflux gave the the quaternary salt as an oil which was dissolved in ethanol and reacted with two equivalents of sodium borohydride. Work up and purification led to a second oil [R_F 0.25 with 1% ammonia in

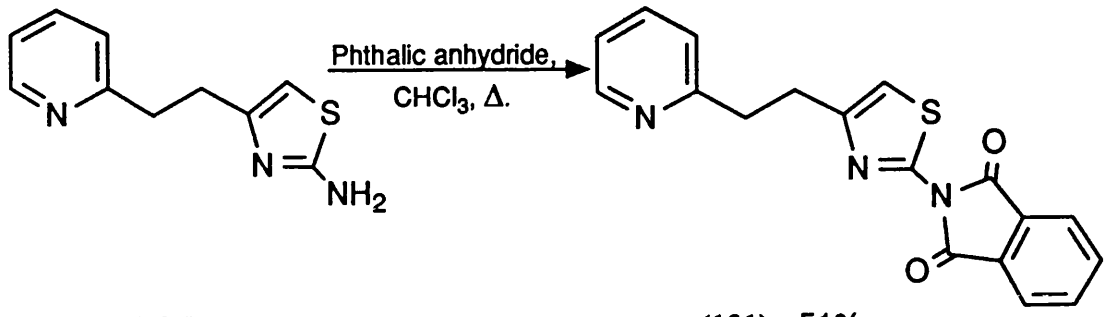
methanol-acetone-dichloromethane (2:3:94) as eluant] in 10% yield over the two steps (scheme 5.15).



Scheme 5.15.

The mass spectrum of this compound has M^+ 299 which indicated that the primary amine (130) had formed, *i.e.* that deprotection had occurred. The ^{1}H n.m.r. spectrum confirmed this assumption, since there are no peaks present which correspond to the resonances of pyrrolyl protons. In fact, there is a broad exchangeable two proton singlet at δ_H 5.18 which is clearly due to the primary amino proton resonances. The remainder of the spectrum was assigned by analogy with the data obtained for the ethyltetrahydropyridine (123). Thus, in the ^{1}H n.m.r. spectrum of the benzyl derivative (130) the doubled multiplets at δ_H 5.60 and δ_H 5.75 due to the tetrahydropyridyl ring vinylic proton resonances present a symmetrical shape, indicating that the unsaturation lies between positions 4" and 5". An interesting feature of the spectrum is the two proton triplet at δ_H 2.60, corresponding to the 1'-H_2 proton resonances, and the multiplet due to the methine proton at position 2", which is now clearly visible at δ_H 2.85. This is not the case in the ^{1}H n.m.r. spectrum of the

ethyltetrahydropyridine (123), in which the 1'-H_2 and 2"-H resonances appear as a complex multiplet (see fig. 5.9).



(125) (131) 51%

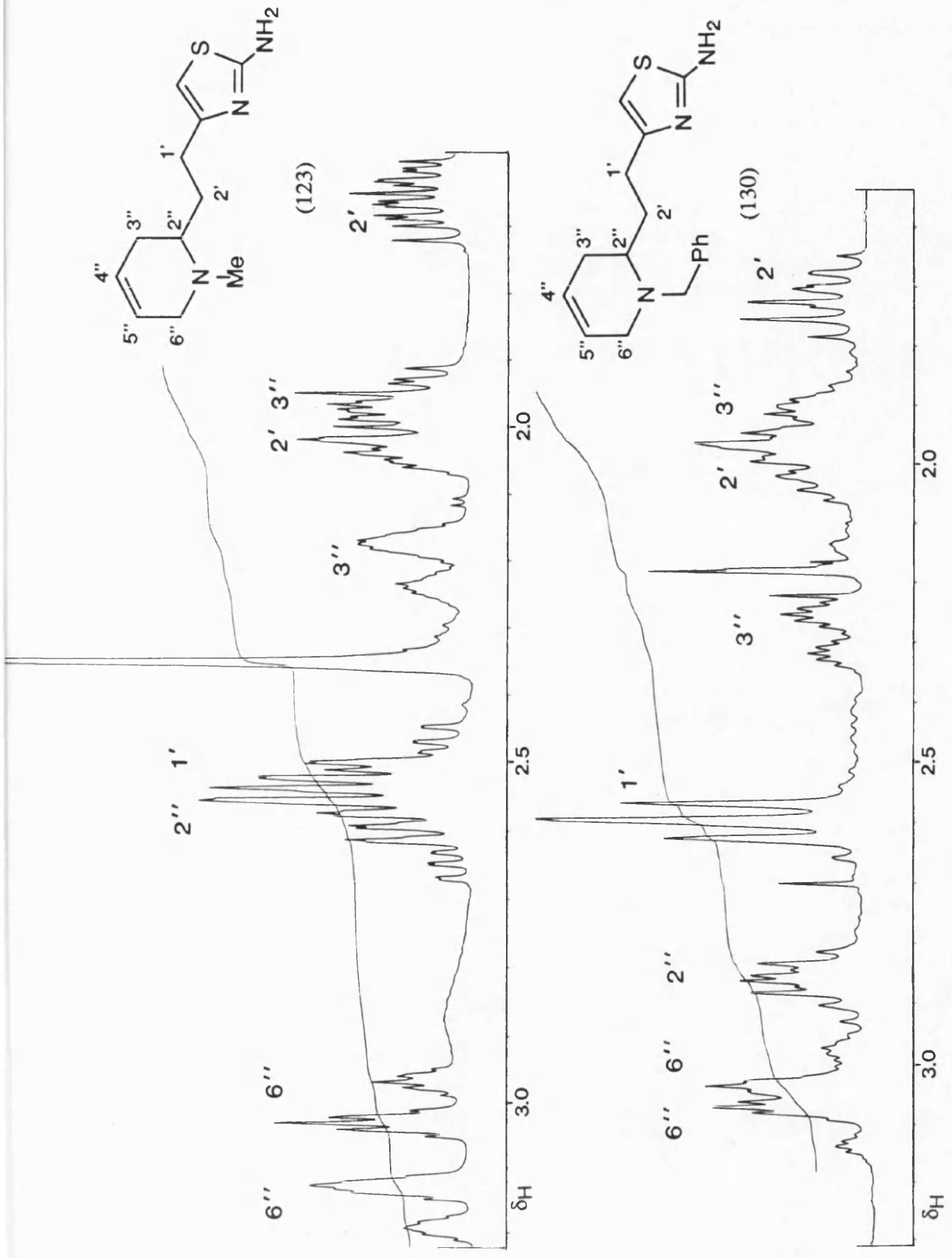
Scheme 5.16.

The result of this experiment is surprising for two reasons. Firstly, we had expected that a saturated side chain substituent at position 2" would allow the formation of the isomeric tetrahydropyridine as well as the observed product (compare the study[5] by Ferles). Secondly, we were disappointed to find that the 2,5-dimethylpyrrolyl protecting group was unstable to the reaction conditions employed during the synthetic sequence, and hence the phthalimide derivative was next prepared.

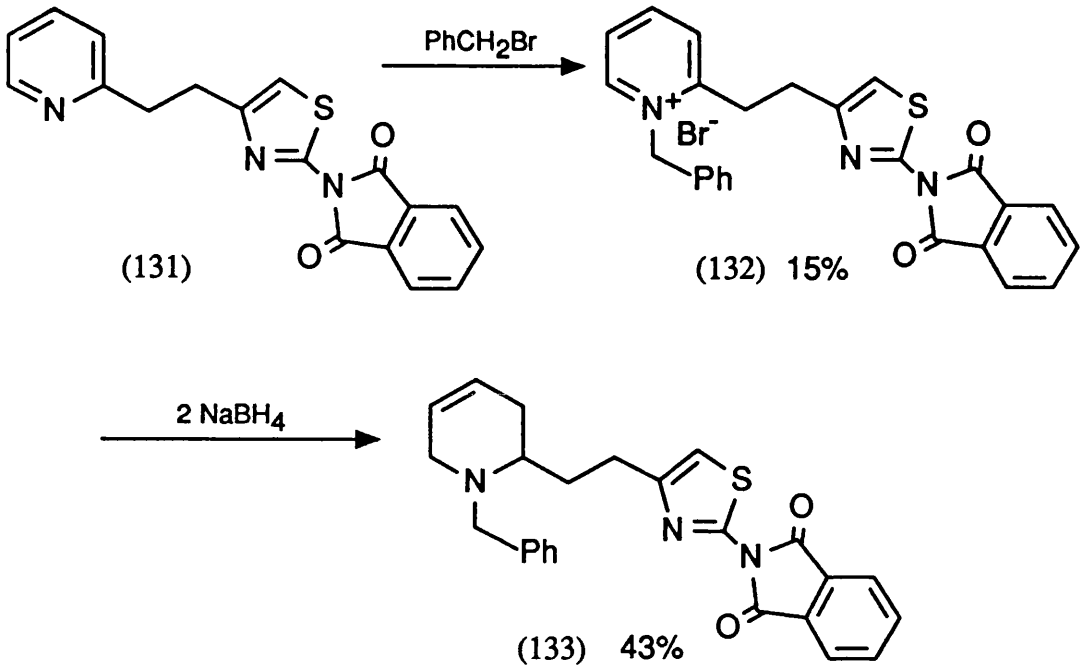
Heating the ethylthiazolamine (125) with phthalic anhydride in chloroform at reflux temperature led to the formation of the phthalimide (131) in 51% yield (scheme 5.16). This compound was treated with an equivalent of benzyl bromide in acetonitrile under reflux. The product was impure, but column chromatography over alumina eluting with 2-propanol-ethyl acetate gave first an orange glass (R_F 0.65, 0.4 M ammonium chloride in methanol) and secondly the quaternary salt (132) as a crystalline solid in relatively low yield (15%, scheme 5.17). Altering the reaction conditions in an effort to increase the yield of the quaternary salt (132) had little or no effect. For example, stirring the phthalimide (131) and benzyl bromide together at room temperature merely resulted in an increased quantity of the orange glass. Despite attempts at purification, we were unable to identify the glass, and we there-

Fig. 5.9.

^{1}H n.m.r. spectra of (123) and (130). (Between δ_H 1.6 and δ_H 3.2 only).



fore continued with the synthetic sequence.



Scheme 5.17.

Sodium borohydride reduction of the quaternary salt (132) led to the isolation of the phthalimide protected ethyltetrahydropyridine (133, scheme 5.17) as a solid in 43% yield. The COSY n.m.r. spectrum of this compound was not only invaluable in confirming that we had correctly assigned the structure of this compound, but also the other ethyltetrahydropyridines that we had so far obtained (fig. 5.10, table 5.3). Thus, there are cross peaks from the 6''-H_2 resonances (δ_H 3.00, δ_H 3.12) to multiplets at δ_H 1.95 and δ_H 2.30. These are clearly due to homoallylic coupling between the resonances of 6''-H_2 and those of the protons at position 3''. There are also cross peaks from the triplet (J 8 Hz) at δ_H 2.71 due to the 1'-H_2 resonances, to multiplets at δ_H 1.76 and δ_H 2.05. The latter signals are therefore due to the resonances of the protons at position 2'. Further, the cross peaks between the resonances at δ_H 1.76 and δ_H 2.05, and also between those at δ_H 1.95 and δ_H 2.30, indicate that each pair of protons is located on the same carbon atom, *i.e.* 2'-C and 3''-C respectively. Finally, a multiplet at δ_H 2.93 exhibits cross peaks to the latter signals (due to 2'-H_2

and 3''-H_2), and is thus assigned as the resonance of 2''-H.

COSY Spectral Data for (133).	
Observed δ_H. (Assignment.)	Cross Peaks (δ_H). (Assignment.)
3.12, 3.00 (6''-H), (6''-H)	2.30, 1.95 (3''-H), (3''-H)
2.93 (2''-H)	2.30, 2.05, 1.95, 1.76 (3''-H), (2'-H), (3''-H), (2'-H)
2.71 (1'-H_2)	2.05, 1.76 (2'-H), (2'-H)
2.30 (3''-H)	1.95 (3''-H)
2.05 (2'-H)	1.76 (2'-H)

Table 5.8.

So far we had found that:

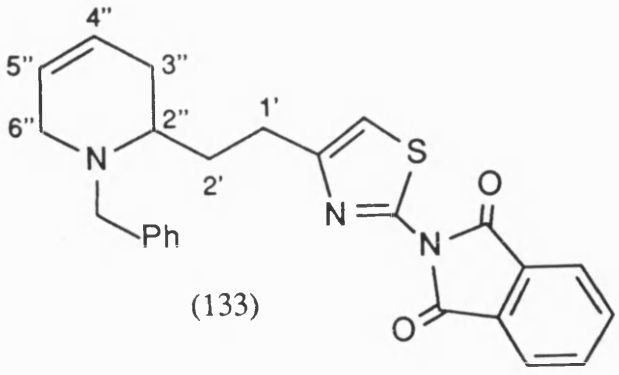
1. The sodium borohydride reduction of a pyridyl quaternary salt with an unsaturated 2-substituent leads to a 1,2,3,6-tetrahydro derivative (120).

2. The sodium borohydride reduction of pyridyl *N*-benzyl bromides with saturated 2-substituents also leads to 1,2,3,6-tetrahydro derivatives (130 and 133).

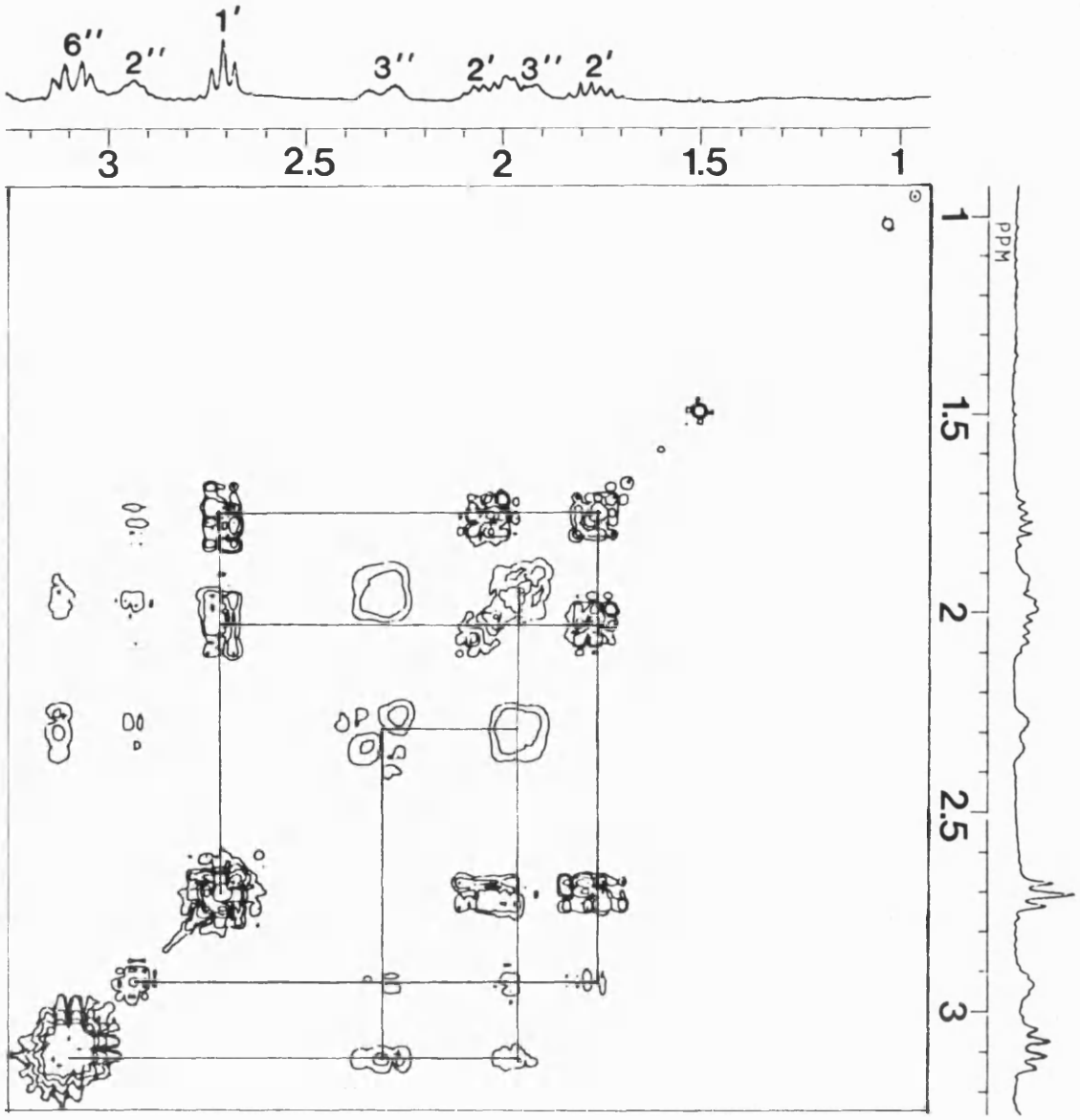
We were therefore interested to discover whether reducing the size of the *N*-alkyl group in the case of the saturated side chain compound would lead to the formation of a 1,2,5,6,-tetrahydro derivative. Hence the phthalimide (131) was heated with iodomethane in acetonitrile. The methiodide (134) crystallised from the cool reaction mixture in high yield (75%), and this was recrystallised from ethanol-methanol to

Fig. 5.10.

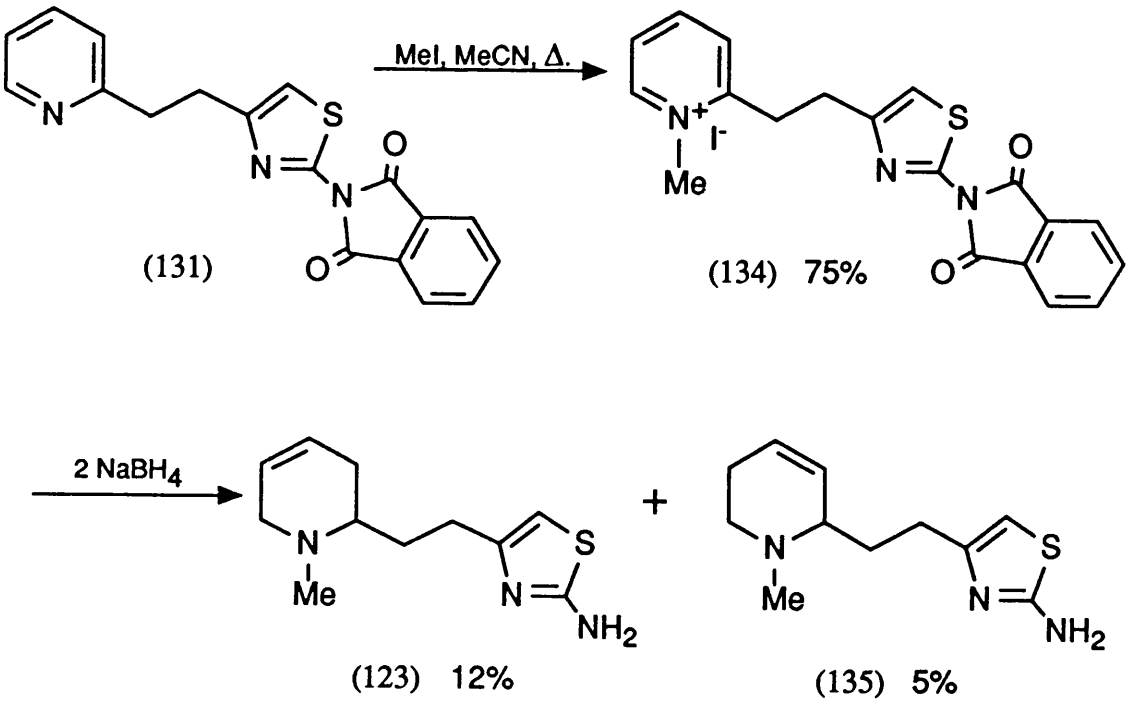
COSY spectrum of (133).



(133)



afford the pure compound (scheme 5.18). [It was interesting to note the high yield and clean reaction to form the methiodide derivative (134), compared with the analogous reaction to form the benzyl bromide (132)]. The methiodide (134) was treated with 2 equivalents of sodium borohydride, and after 1h the normal work-up procedure was followed. Thus, the solvents were removed *in vacuo*, the residue was acidified, then basified, and extracted with ethyl acetate. We were very surprised to find that t.l.c. analysis of the organic extracts showed no sign of any products. The aqueous washings were therefore concentrated by azeotropically removing the water in the presence of 2-propanol. The resulting residue was chromatographed over silica gel to afford an oil (1 g). The ^1H n.m.r. spectrum of this oil indicated that we had isolated a mixture of the tetrahydropyridine isomers (123) and (135). For example, singlets at δ_H 6.08 and δ_H 6.14 (integral ratio 1:3) appeared to correspond to the respective 5-H thiazole proton resonances. Also, the vinylic region (δ_H 5.55-5.95) showed a complex set of peaks, although it was interesting to note that there were no peaks due to phthalimide proton resonances.



Scheme 5.18.

It was possible to separate the compounds present in the mixture by the use of preparative centrifugally accelerated thin layer radial chromatography, and on a larger scale with "flash" chromatography. Using these techniques, we isolated a product [R_F 0.45, 1% NH_3 in methanol–acetone–chloroform (2:3:10)] which exhibited spectral data identical to that of the tetrahydropyridine (123). The other compound isolated, also with R_F 0.45, and with the same molecular mass as the tetrahydropyridine (123), was identified by analysis of its spectral data. In particular, extensive use was made of the various high field n.m.r. techniques available to us.

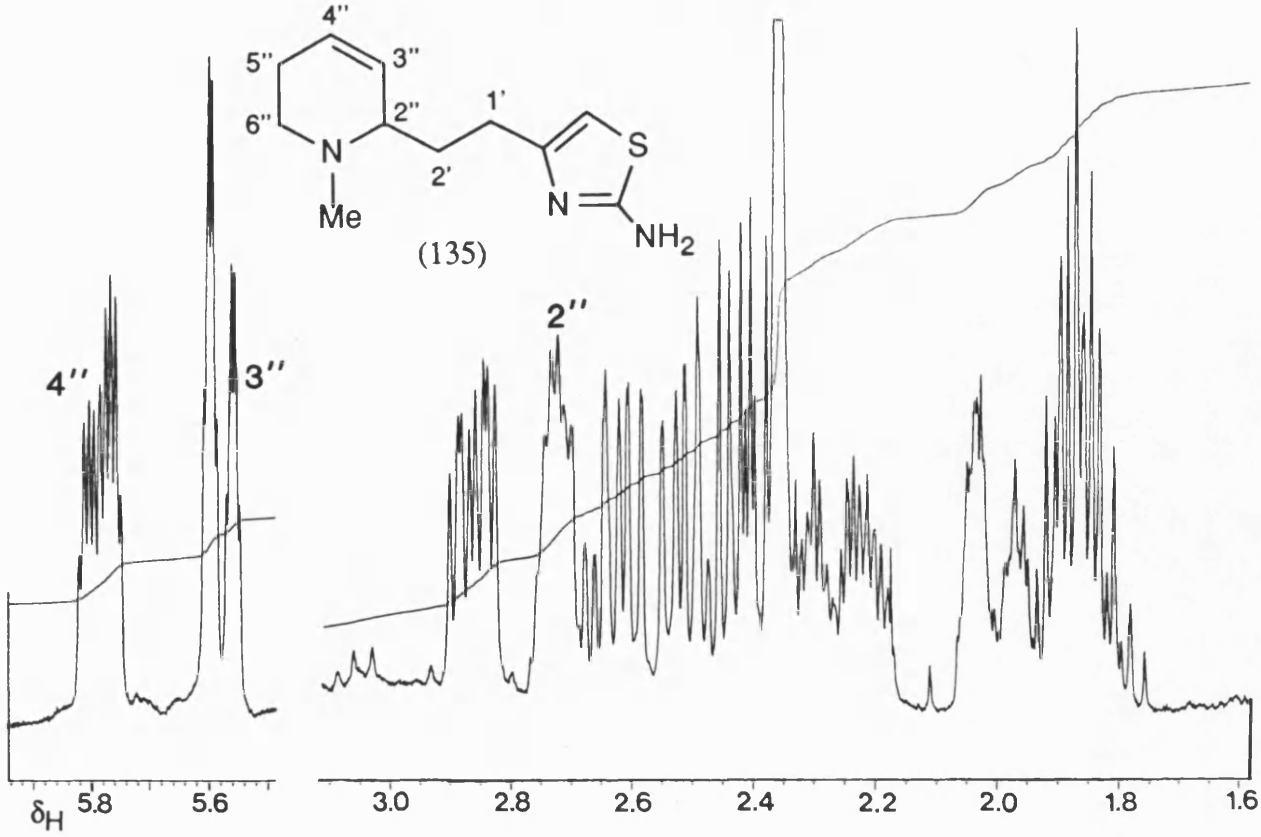
Whilst the ^1H n.m.r. spectrum is complex, (fig. 5.11), the ^{13}C n.m.r. spectrum is comparatively straightforward to assign, assuming that the compound is the isomeric tetrahydropyridine (135). Thus, from literature data[7] the peaks at δ_C 129.2 and δ_C 125.4 were assigned as the 3"-C and 4"-C resonances respectively. Also, a doublet at δ_C 61.3 is clearly due to the resonance of 2"-C. Next, the C–H correlation spectrum (fig. 5.12, table 5.4) gave us a starting point in the ^1H n.m.r. spectrum. Hence, there are cross peaks from the resonances at δ_C 129.2 and δ_C 125.4 to peaks at δ_H 5.58 and δ_H 5.80 respectively. The latter peaks are therefore assigned as the 3"-H and 4"-H resonances. Another obvious cross peak is between the resonances at δ_C 61.3 and δ_H 2.72 and we may thus assign the latter as being due to 2"-H.

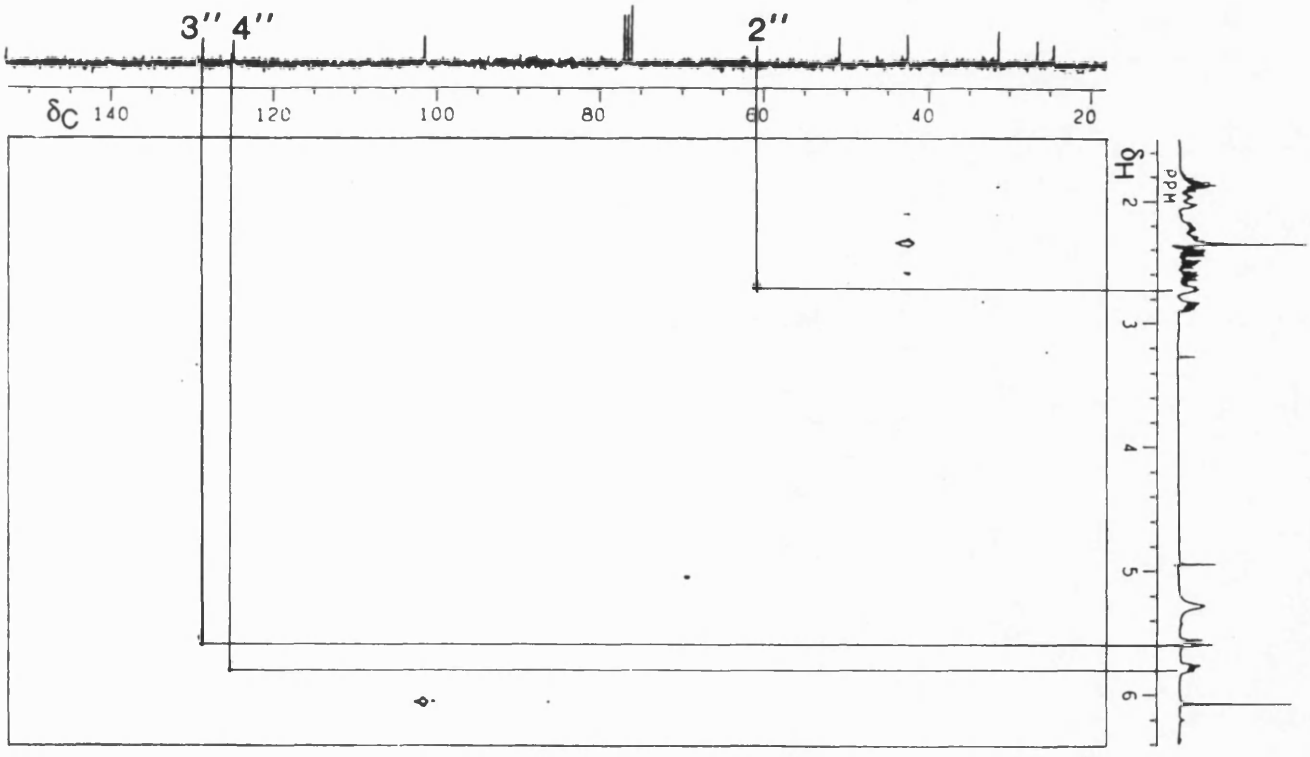
C-H Correlation Data for (135).

δ_C	δ_H	Assignment.
61.3	2.72	2"
129.2	5.58	3"
125.4	5.80	4"

Table 5.4.

Fig. 5.11. ^{1}H n.m.r. spectrum of (135). (δ_H 1.6-δ_H 3.0 and δ_H 5.55-δ_H 5.85).





C-H Correlation spectrum of (135).

Fig. 5.12.

We were now in a position to analyse the ^1H n.m.r. spectrum by using the decoupling difference technique. The results are summarised in table 5.5. Irradiation of the resonance at δ_H 5.80 (4''-H) gives enhancements at δ_H 2.00, δ_H 2.27, δ_H 2.72 and δ_H 5.58. Hence it is coupled to the resonances of adjacent protons at 3''-H and 5'' -H_2 (δ_H 5.58, δ_H 2.00, and δ_H 2.27 respectively) and also exhibits allylic coupling to the resonance at δ_H 2.72 due to 2''-H. The irradiated resonance at δ_H 5.58 (3''-H) gives its strongest enhancements at δ_H 5.80 (4''-H) and δ_H 2.72 (2''-H). There is also weaker enhancement of the signal at δ_H 2.27 (5''-H) due to allylic coupling. A different pattern is shown by the irradiation of the resonance at δ_H 2.87. The strongest enhancement occurs at δ_H 2.43, but there is also enhancement of the signals at δ_H 2.00 and δ_H 2.27 (5''-H_2), whilst the remainder of the spectrum shows zero enhancement. The peak at δ_H 2.87 is thus assigned as being due to the resonance of a proton at position 6'', the geminal resonance appearing at δ_H 2.43. Finally, irradiation of the resonance at δ_H 2.72 gives enhancements as expected at δ_H 5.80, δ_H 5.58, and also at δ_H 1.87, indicating that the latter resonance is due to 2'-H_2.

Decoupling Difference Spectral Data for (135).			
Decoupled resonance (δ_H).	Enhancement (δ_H).	Zero enhancement (δ_H).	Assignment.
5.80	5.58, 2.72, 2.27, 2.00	2.87, 2.4-2.7, 1.87	4''-H
5.58	5.80, 2.72, 2.27	2.87, 2.4-2.7, 1.87	3''-H
2.87	**2.43**, (2.27, 2.00)	5.80, 5.58, 1.87	6''-H_1
2.72	**5.80**, **5.58**, 1.87	---	2''-H

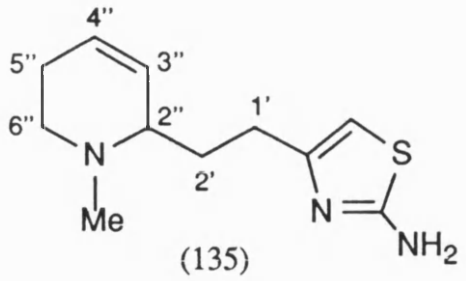
Table 5.5.

KEY: **strong**, medium, (weak) enhancements.

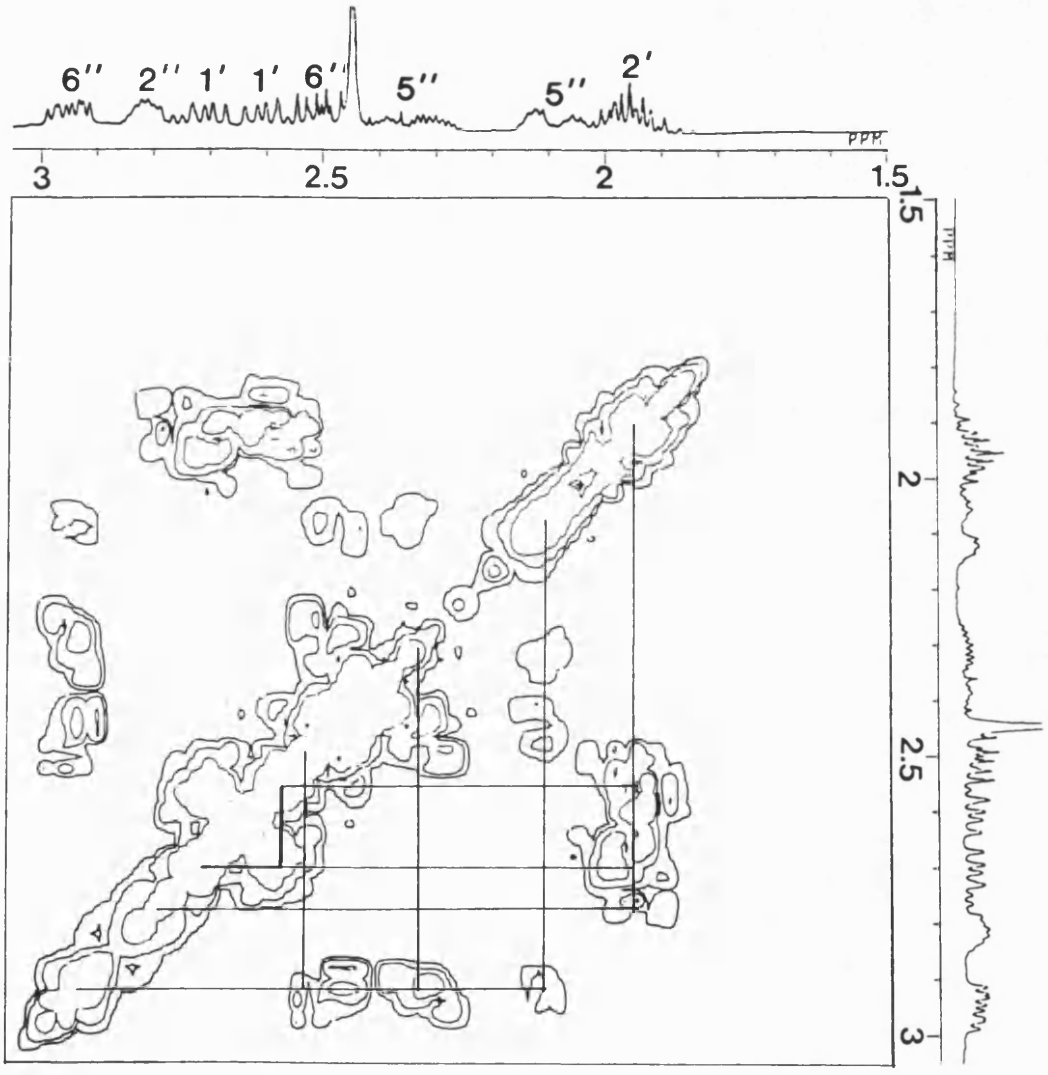
Confirmatory evidence was obtained from the COSY spectrum (fig. 5.13, table

Fig. 5.13.

COSY spectrum of (135).



(135)



5.6) particularly the region between δ_H 1.8 and δ_H 3.00.

COSY Spectral Data for (135).	
Observed δ_H. (Assignment.)	Cross Peaks (δ_H). (Assignment.)
2.87 (6''-H)	2.43, 2.27, 2.00 (6''-H), (5''-H), (5''-H)
2.72 (2''-H)	1.87 (2'-H_2)
2.62 (1'-H)	2.52, 1.87 (1'-H), (2'-H_2)
2.52 (1'-H)	2.62, 1.87 (1'-H), (2'-H_2)
2.43 (6''-H)	2.27, 2.00 (5''-H), (5''-H)
2.27 (5''-H)	2.00 (5''-H)
1.87 (2'-H_2)	2.72, 2.62, 2.52 (2''-H), (1'-H), (1'-H)

Table 5.6.

The points to note in particular from the COSY data are the cross peaks between the resonances due to 5''-H_2 and 6''-H_2 and also the cross peaks between the resonances at δ_H 2.52, δ_H 2.62 (1'-H_2) and δ_H 1.87 (2'-H_2). Thus we can be confident in our structural assignment, and have thus proved that it is possible to obtain a 2-substituted 1,2,5,6-tetrahydropyridine by choosing the correct substrate for reduction.

References.

1. D. M. Stout and A. I. Meyers, *Chem. Rev.*, 1982, **82**, 223.
2. U. Eisner and J. Kuthan, *Chem. Rev.*, 1972, **72**, 1.
3. R. E. Lyle and P. S. Anderson, *Adv. Heterocycl. Chem.*, 1966, **6**, 45.
4. M. Ferles and J. Pliml, *Adv. Heterocycl. Chem.*, 1970, **12**, 43.
5. M. Holik and M. Ferles, *Collect. Czech. Chem. Commun.*, 1967, **32**, 3067.
6. P. S. Anderson and R. E. Lyle, *Tetrahedron Lett.*, 1964, 153.
7. E. Pretsch, T. Clerc, J. Seibl, and W. Simon, *Tables of Spectral Data for Structure Determination of Organic Compounds,* Springer, Berlin, English ed. (1983).
8. R. B. Woodward, G. Volpp, and J. Z. Gougoutas, *The Harvey Lectures*, 1963, 31.
9. S. Hunig, H. R. Muller, and W. Thier, *Angew. Chem., Int. Ed. Engl.*, 1965, **4**, 271.
10. C. E. Miller, *J. Chem. Educ.*, 1965, **42**, 254.
11. K. Kondo, S. Murai, and N. Sonoda, *Tetrahedron Lett.*. 1977, **18**, 3727.
12. J. M. Hoffmann and R. H. Schlessinger, *J. Chem. Soc., Chem. Commun.*, 1971, 1245.
13. D. J. Hart and K. Kanai, *J. Org. Chem.*, 1982, **47**, 1555.
14. K. Mori, M. Ohki, A. Sato, and M. Masui, *Tetrahedron*, 1972, **28**, 3739.
15. J. W. Hamersma and E. I. Snyder, *J. Org. Chem.*, 1965, **30**, 3985.
16. J. Thiele, *Liebigs Ann. Chem*, 1892, **271**, 127.
17. N. J. Cusack, C. B. Reese, A. C. Risius, and B. Roozpeikar, *Tetrahedron*, 1976, **32**, 2157.

18. D. H. R. Barton and S. W. McCombie, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1574.

19. M. Yamashita, Y. Kato, and R. Suemitsu, *Chem. Lett.*, 1980, 847.

20. K. Ramasamy, S. K. Kalyanasundaram, and P. Shanmugam, *Synthesis*, 1978, 545.

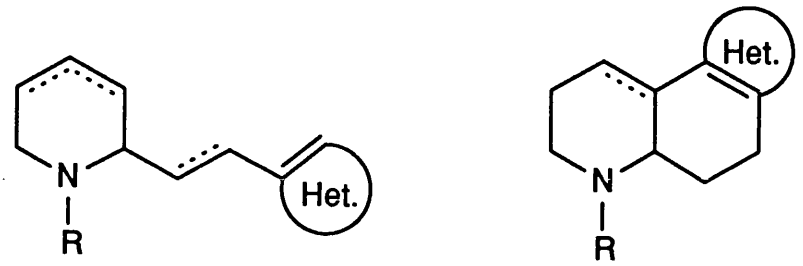
21. A. J. Birch and K. A. M. Walker, *Tetrahedron Lett.*, 1967, **8**, 1935.

22. J. C. Jaen, L. D. Wise, H. Tecle, and S. C. Bergmeier. (Warner–Lambert Co.), U.S. US 4 650 805.

23. S. P. Bruekelman, S. E. Leach, G. D. Meakins, and M. D. Tirel, *J. Chem. Soc., Perkin Trans. 1*, 1984, 2801.

6. Further Studies in the Chemistry of 2-Thiazolamines.

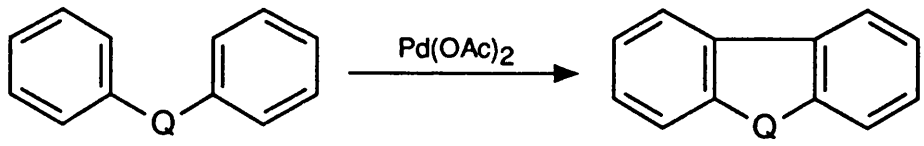
An important objective of our work was to effect the cyclisation of compounds such as (39) to the tricyclic products of the type (32, fig. 6.1).



(39) (32)

Fig. 6.1.

The oxidative cyclisation of various bis-aryl systems has been studied by several groups of workers. For example, Akermark and coworkers used a palladium initiated cyclisation in the transformation of compounds of the general structure (136) to give the products (137,scheme 6.1).[1] Under similar conditions, Itahara was able to cyclise the indole derivative (138) to yield the tetracyclic compound (139, scheme 6.2).[2,3] We therefore hypothesised that a palladium mediated cyclisation might be appropriate to our systems.



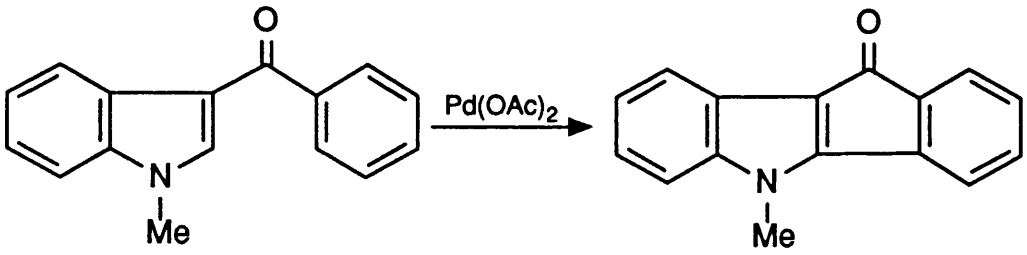
Q= O, S, NAc

(136) (137)

Scheme 6.1.

In an early experiment, the ethylisoxazole (83, fig. 6.2) was heated with palladium acetate in trifluoroacetic acid for several hours in anticipation of forming (140, fig. 6.2). However, this treatment led to the decomposition of starting material with

no trace of product. A similar result was obtained for the ethylthiazolamine (125).



(138) (139)

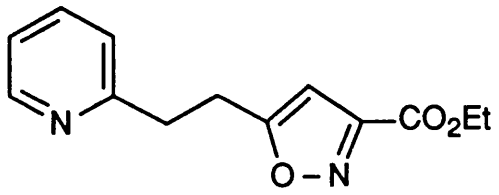
Scheme 6.2.

Bromine or iodine atoms situated on one or both of the aromatic rings are known to facilitate some palladium induced coupling reactions. We therefore decided to prepare the 4-bromo derivative (141, fig. 6.2) of the ethylthiazolamine (125). Since an initial attempt at halogenation with bromine in acetic acid was unsuccessful, perhaps because of salt formation, we turned to an alternative method, where acidic conditions are avoided. 2,4,4,6-Tetrabromocyclohexa-2,5-dienone (142, fig. 6.2) has been used to brominate aromatic amines, although there is no record of its use with heterocycles.[4] We found that with this reagent the 4-bromothiazolamine (141) was produced in 56% yield. (This product decomposes fairly rapidly at room temperature, and is not easily chromatographed).

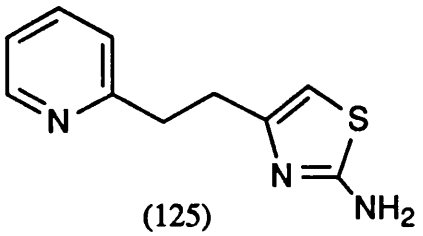
The 4-bromothiazolamine was heated with palladium acetate in acetic acid under reflux, but as before nothing corresponding to the required compound was identified in the reaction mixture.[A sample of the product (143, fig. 6.2) obtained by the route outlined in scheme 1.2 (page 22) was supplied by Organon for comparison].

At this point we turned our attention to the reduced compounds. In particular, we considered that a cyclisation might be accomplished *via* an epoxide derivative of the general structure (144) or (145, scheme 6.3). This might be possible either by direct reaction of the 2-thiazolamine moiety with the epoxide, or by ring opening, followed by reaction with the allylic alcohol derivative (146).

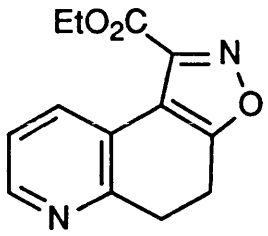
Lyle[5, 6] has prepared epoxides of the type (147) and subsequently ring opened



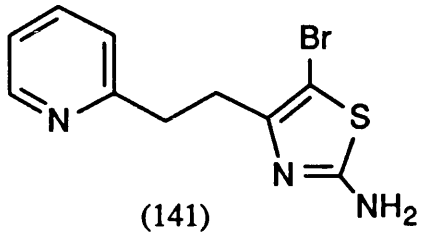
(83)



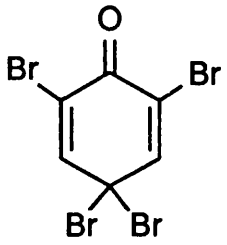
(125)



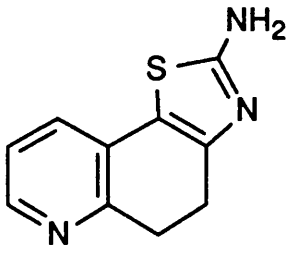
(140)



(141)



(142)

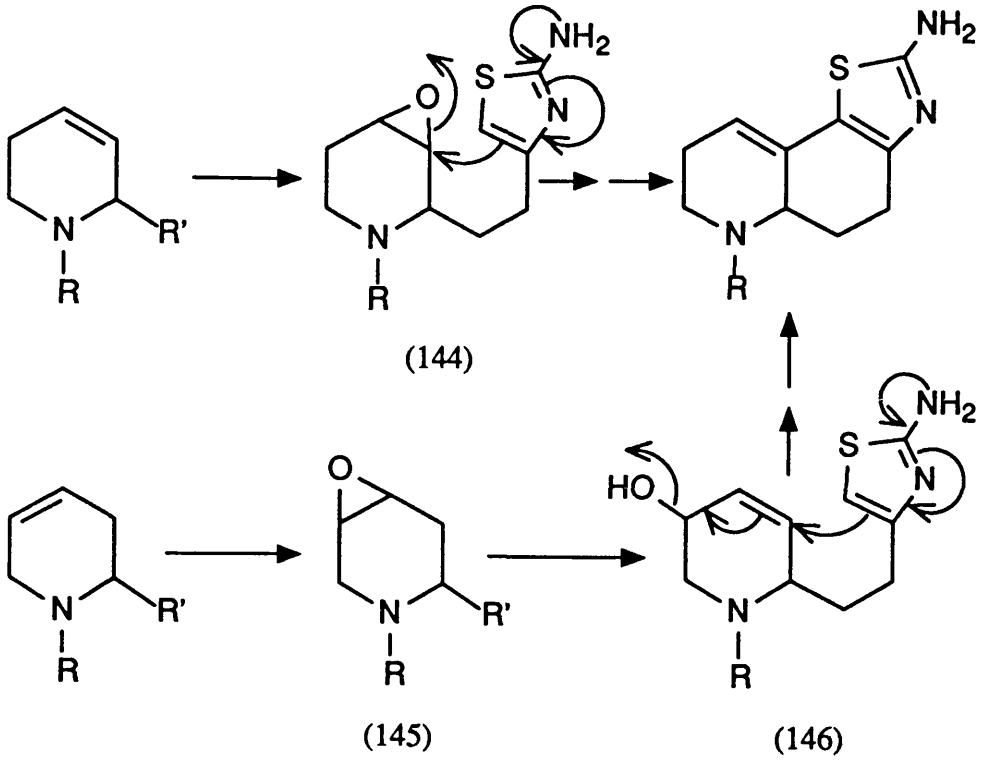


(143)

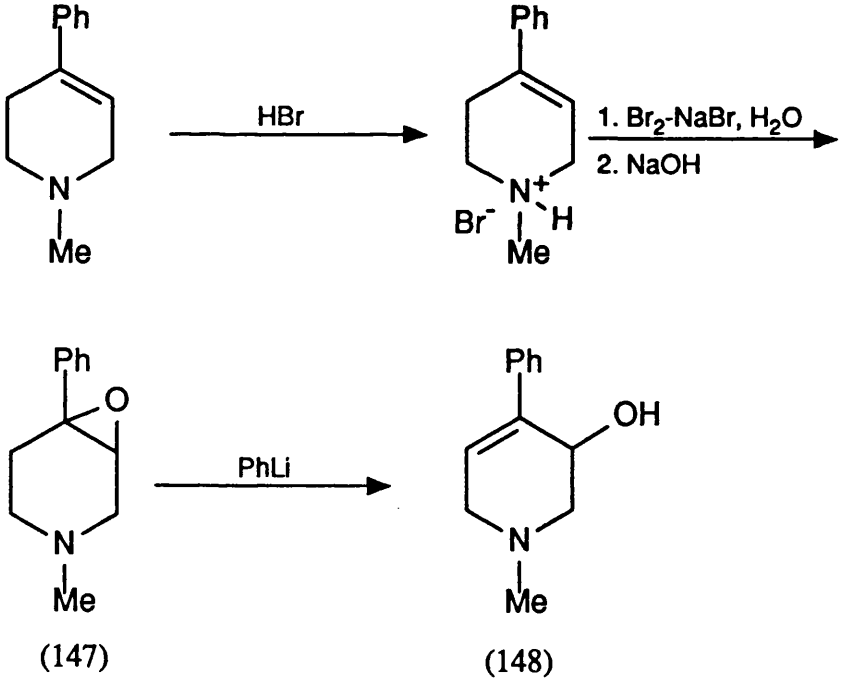
Fig. 6.2.

them to the corresponding allylic alcohols (148, scheme 6.4). The transformation was accomplished by the action of an aqueous solution of bromine and sodium bromide on the tetrahydropyridine hydrobromides, followed by treatment with aqueous sodium hydroxide.

Thus we used these conditions in an attempt to epoxidise the tetrahydropyridines (130) and (123, fig. 6.3). In each case the hydrobromides were formed *in situ* and these were each treated with an aqueous solution of bromine and sodium bromide. Work-up in both cases resulted in the recovery of starting materials with polar decomposition products. A similar result was obtained when the phthalimide (133) was subjected to bromination-hydrolysis conditions.



Scheme 6.3.



Scheme 6.4.

Another method of preparation of epoxides is by the use of a peracid such as *m*-CPBA. With our substrates this reaction is complicated by the presence of amino functions in the molecule which are readily converted to *N*-oxides by peracids. Thus,

attempted epoxidation of the phthalimide (133) and the ethyltetrahydropyridine (120) in *t*-BuOH/CH_2Cl_2 led to polar products which decomposed on attempted purification.

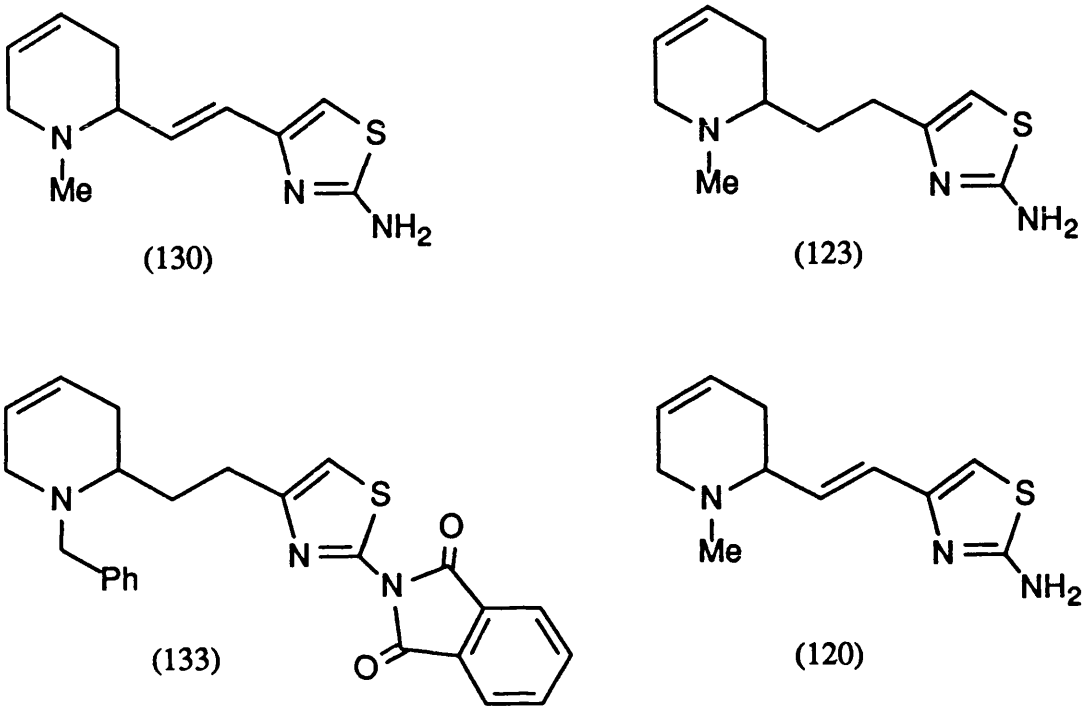
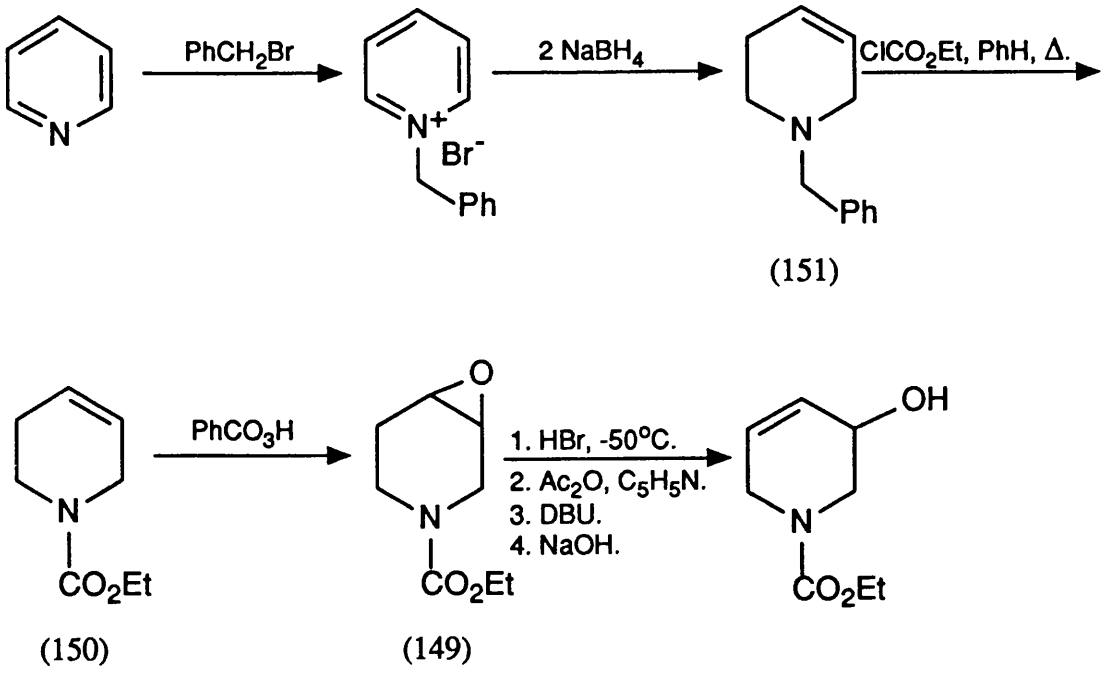


Fig. 6.3.

In subsequent work we sought to minimise side reactions, and therefore decided to investigate the chemistry of carbamyl derivatives. There is good literature precedent for this; for example, epoxides of the type (149) have been reported.[7] These compounds were prepared by the action of perbenzoic acid on the protected tetrahydropyridine (150), which was obtained from the benzylamine (151, scheme 6.5). We considered that the protection of the tetrahydropyridyl ring amino function as a carbamate in our compounds would allow the formation of the corresponding epoxide and exclude *N*-oxide formation and ring opening.

In the literature study cited above, the conversion to the carbamate (150) was achieved by heating the benzylamine with ethyl chloroformate in benzene under reflux. When these conditions were applied to our substrate (133), however, only



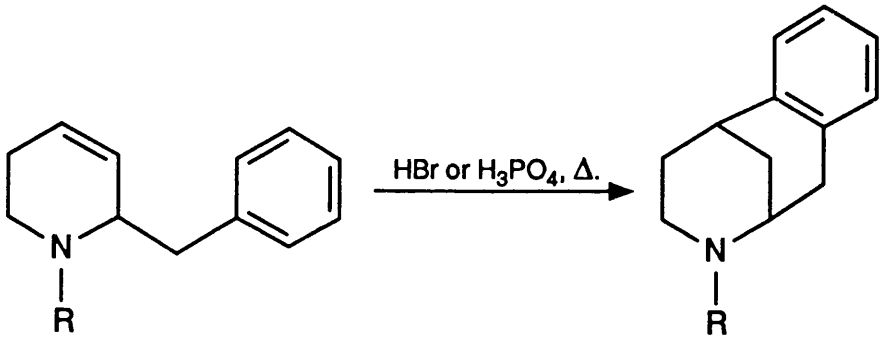
Scheme 6.5.

starting material was isolated. Repeating the procedure using toluene as the solvent, and an extended period of reflux similarly had no effect. Neither did the use of methyl chloroformate or trichloroethyl chloroformate.[8]

Since the direct production of the carbamate had been unsuccessful we decided that deprotection of the benzyl group, followed by the reaction of the resulting secondary amine with a chloroformate would be the most efficient method of producing the carbamate. The most generally used method for the deprotection of benzyl groups is catalytic hydrogenation. This could not be used with our compounds because of the effect of the thiazole sulphur atom, which seems to act as a catalyst poison. Alternative methods of *N*-dealkylation include the use of sodium in ammonia, and reaction with iodotrimethylsilane.[9-11] Both of these methods were attempted with the benzylamine (133), but neither gave the required compound, starting material being recovered in both cases.

Strongly acidic conditions are known to induce cyclisation in some compounds. For example, 2-benzyltetrahydropyridines (152) undergo "Grewe"-type cyclisation

with hydrobromic or phosphoric acid to give the corresponding benzomorphans (153).[12] A similar reaction might be envisaged with our compounds (123, 135) to yield either the six or seven membered ring derivatives. Heating the ethyltetrahydropyridines (123) and (135) in 48% hydrobromic acid under reflux led to the destruction of the compounds, and this is a further indication of the sensitive nature of our substrates.

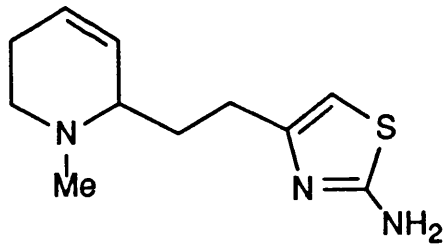


(152) (153)

Scheme 6.6.

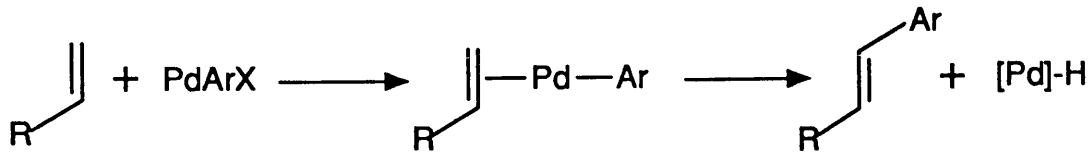
By this time we had been able to prepare a pure sample of the 1,2,5,6-tetrahydropyridine (135) and we therefore decided to examine palladium induced methods of aryl-alkene coupling.[13] The Heck reaction is a general method involving the *cis* addition of a η^1-Ar[Pd] species across a double bond.[14-16] In cases where this generates a β-hydrogen *syn* to the [Pd], elimination of H-[Pd] occurs to give a new alkene (scheme 6.7). Regioselectivity depends on both steric and electronic factors. For example, it has been reported that the coupling of bromobenzene to styrene (154) with palladium occurs exclusively at 2-C to give *trans* stilbene (90, scheme 6.8).[14] Similarly, the palladium acetate induced reaction between styrene and benzene results in the formation of *trans* stilbene (90, scheme 6.8).[17]

Heterocyclic compounds are also known to undergo the Heck reaction. For example, Japanese workers were able to alkenate furans, thiophenes and indoles with various alkenes to give the corresponding *transoid* products (155, scheme 6.9).[18] Similarly, in a recent synthesis[19] French workers coupled bromofurans and

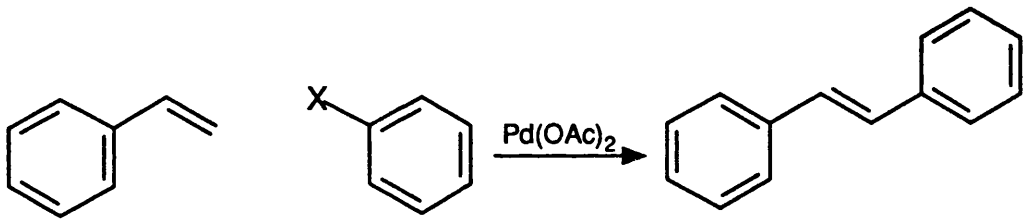


(135)

Fig. 6.4.

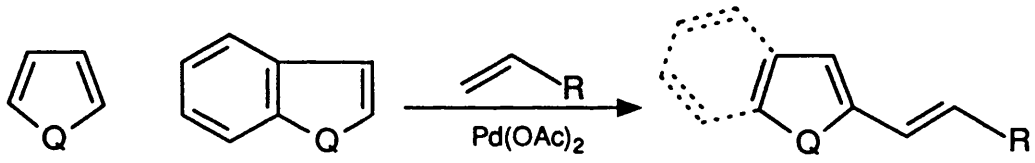


Scheme 6.7.



(154) X=Br, H. (90)

Scheme 6.8.

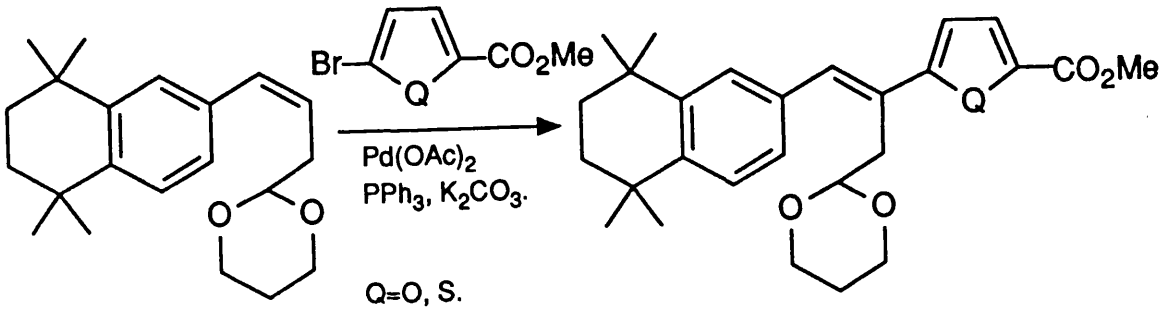


Q=S, O Q=O, NR' (155)

Scheme 6.9.

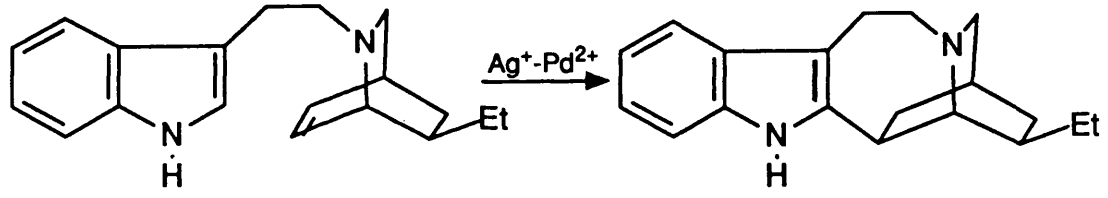
bromothiophenes with a *cis* disubstituted alkene using Heck-type conditions (scheme 6.10).

Although some aromatic species require a halogen atom (Br, I) or a metal substituent to direct the initial palladation step, with heterocycles this is not always necessary. Recently, there have been several reported examples of intramolecular Heck reactions.[20–23] For example, Trost has used a Pd^{2+}–Ag^{+} mixed metal system to



Scheme 6.10.

cyclise alkaloids of the general structure (156, scheme 6.11).[24, 25] This reaction appeared to be of particular relevance to our system since it was carried out on a substrate bearing a tertiary amino function. Unfortunately, when we used these conditions with the tetrahydropyridines (123) and (135) as the substrates, work-up and purification led to the isolation of starting materials only.

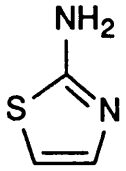


(156)

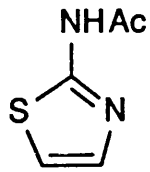
Scheme 6.11.

The palladium induced alkenylation of thiazoles has not been reported. Thus, in order to determine whether this type of reaction would be viable, we decided to perform a model study using 2-thiazolamine (157, fig. 6.5) and styrene (154). These compounds were heated together in acetic acid under reflux for 8h with palladium acetate (1 eq.). An excess of 2-thiazolamine (157) was used to reduce the likelihood of oxidative coupling of the alkene, producing butadiene derivatives. Work-up and purification led to a mixture of compounds of identical R_F values which appeared to contain 2-thiazolacetamide (158, fig. 6.5) and another product which showed aromatic resonances in the ^1H n.m.r. spectrum. Encouraged by this result, we repeated the reaction, this time using 2-thiazolacetamide (158) and styrene (154)

(1:1), palladium acetate (0.15 eq.) and copper acetate (2 eq.) as an oxidant for the palladium (scheme 6.12). After 8h under reflux in acetic acid we were able to obtain a pure product from this reaction, although the yield was not high (30%).



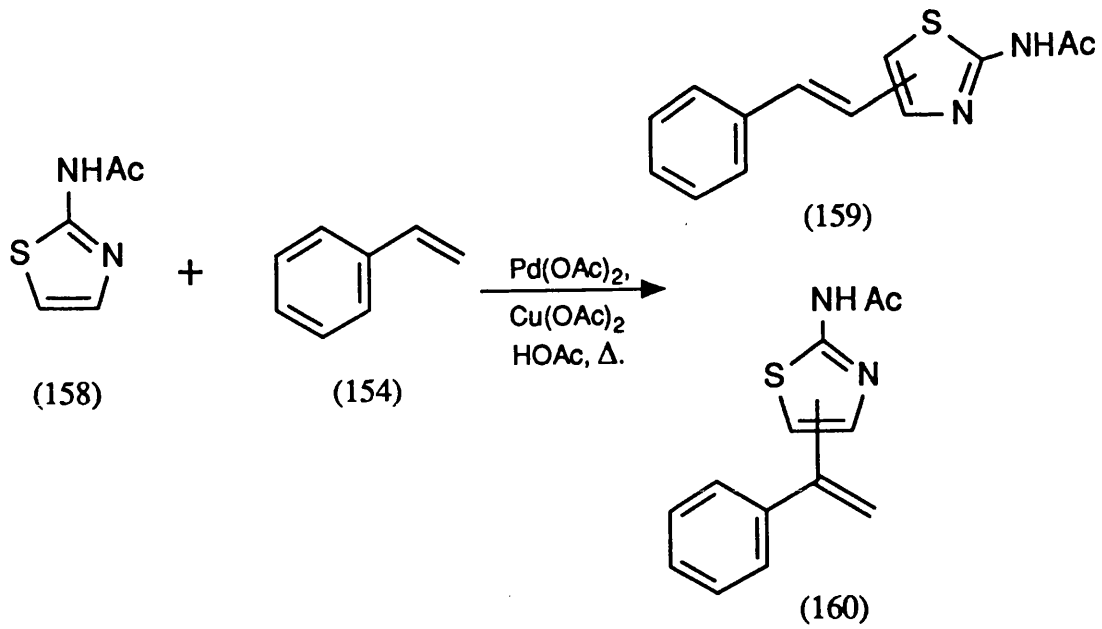
(157)



(158)

Fig. 6.5.

Spectral data suggest that it is the product resulting from the coupling of 2-thiazolacetamide and styrene, *i.e.* either (159) or (160) (M^+, 244) (scheme 6.12). Thus, the ^1H n.m.r. spectrum contains peaks due to the resonances of phenyl protons (δ_H 7.40) and also a 3-proton singlet at δ_H 2.26 due to the amide methyl resonance. Interestingly, the vinyl proton resonances appear as two singlets at δ_H 5.30 and δ_H 5.54. This strongly indicates that coupling has occurred at 1'-C to give the product (160), since the alternative 1', 2'-*trans* disubstituted compound (159) would exhibit a pair of doublets (J 16 Hz) in the ^1H n.m.r. spectrum. Confirmation of our hypothesised structure was obtained from the ^{13}C n.m.r. spectrum, in which a triplet at δ_C 115.0 corresponds to the resonance of the methylene carbon (2'-C). We next had to determine the position of coupling on the thiazole ring. The most active position of thiazoles for electrophilic attack, and therefore the most likely to have coupled (after the blocked 2 position) is 5-C.[26, 27] Examination of the ^1H n.m.r. spectral data indicated that this was the case, since there are no peaks in the region δ_H 6.1-7.1 which would correspond to the resonance of 5-H. Also, the ^{13}C n.m.r. spectrum exhibits a singlet at δ_C 126.5, assigned as the resonance of 5-C, and a doublet at δ_C 134.8 corresponding to the resonance of 4-C. Thus, structure (161) is correct. The u.v. spectral data for this compound are presented in a table in the appendices for comparison with other related molecules.



Scheme 6.12.

Using the coupling conditions we had developed for the intermolecular reaction (scheme 6.12) with the tetrahydropyridine (135) and the acetamide [162, fig. 6.6, obtained from the acetylation of (135) with acetic anhydride in 88% yield], did not however result in the cyclisation of the compounds. This may be due to the presence of the tertiary amino function in the molecule, which we hoped would be protonated and therefore protected under the reaction conditions. We have nonetheless demonstrated the utility of a palladium mediated thiazole-alkene coupling reaction, which has potential for use in other syntheses.

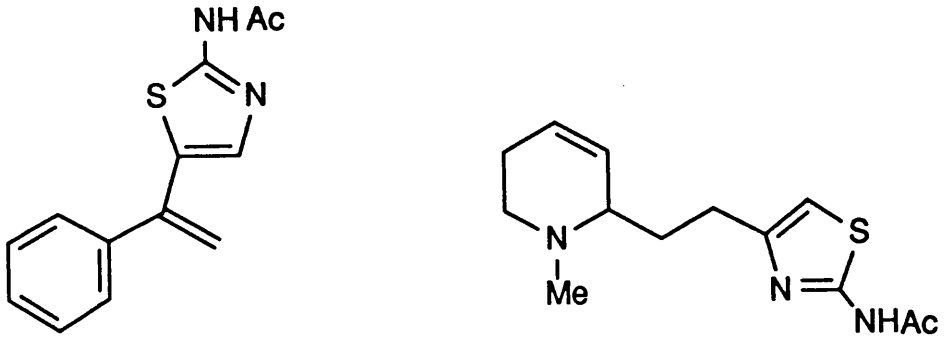


Fig. 6.6.

References.

1. B. Akermark, E. Eberson, E. Jonsson, and E. Petterson, *J. Org. Chem.*, 1975, **40**, 1365.
2. T. Itahara, *Synthesis*, 1979, 151.
3. T. Itahara and T. Sakibara, *Synthesis*, 1978, 607.
4. V. Calo, F. Ciminale, L. Lopez, and P. E. Todesco, *J. Chem. Soc. (C)*, 1971, 3652.
5. R. E. Lyle and W. E. Krueger, *J. Org. Chem.*, 1967, **32**, 3613.
6. R. E. Lyle and W. E. Krueger, *J. Org. Chem.*, 1965, **30**, 394.
7. T. Imanishi, H. Shin, M. Hanaoka, T. Momose, and I. Imanishi, *Chem. Pharm. Bull.*, 1982, **30**, 3617.
8. R. A. Olofson, R. C. Schnur, L. Bunes, and J. P. Pepe, *Tetrahedron Lett.*, 1977, **18**, 1567.
9. M. E. Jung and M. A. Lyster, *J. Am. Chem. Soc.*, 1977, **99**, 968.
10. T-L. Ho and G. Olah, *Synthesis*, 1977, 417.
11. T. Morita, Y. Okamoto, and H. Sakurai, *J. Chem. Soc., Chem. Commun.*, 1978, 874.
12. D. C. Palmer and M. J. Strauss, *Chem. Rev.*, 1977, **77**, 1.
13. S. G. Davies, *Organotransition metal chemistry: applications to organic synthesis*, Pergamon, Oxford.
14. R. F. Heck, *Acc. Chem. Res.*, 1979, **12**, 146.
15. R. F. Heck, *J. Am. Chem. Soc.*, 1969, **91**, 6707.
16. R. F. Heck, *J. Am. Chem. Soc.*, 1968, **90**, 5518.

17. Y. Fujiwara, I. Moritani, S. Danno, R. Asano, and S. Teranishi, *J. Am. Chem. Soc.*, 1969, **91**, 7166.

18. Y. Fujiwara, O. Maruyama, M. Yoshidomi, and H. Taniguchi, *J. Org. Chem.*, 1981, **46**, 851.

19. J. Eustache, J-M. Bernardon, and B. Shroot, *Tetrahedron Lett.*, 1988, **29**, 4409.

20. M. M. Abelman, T. Oh, and L. E. Overman, *J. Org. Chem.*, 1987, **52**, 4130.

21. W. G. Early, E. J. Jacobsen, G. P. Meier, T. Oh, and L. E. Overman, *Tetrahedron Lett.*, 1988, **29**, 3781.

22. W. G. Early, T. Oh, and L. E. Overman, *Tetrahedron Lett.*, 1988, **29**, 3785.

23. P. C. Amos and D. A. Whiting, *J. Chem. Soc., Chem. Commun.*, 1987, 510.

24. B. M. Trost and J. M. D. Fortunak, *Organometallics*, 1982, **1**, 7.

25. B. M. Trost, S. A. Godleski, and J. P. Genet, *J. Am. Chem. Soc.*, 1978, **100**, 3930.

26. M. Sainsbury, *Rodd's Chemistry of Carbon Compounds,* 4C, Elsevier, Amsterdam (1986).

27. A. R. Katritzky and C. W. Rees Eds., *Comprehensive Heterocyclic Chemistry*, 1984, **6**, 235, Pergamon.

EXPERIMENTAL.

7.1 General.

Solvents and Reagents.

"Petrol (60–80°C)" refers to that fraction of petroleum ether boiling in the range 60–80°C, which was distilled prior to use. THF was distilled under an atmosphere of nitrogen after drying with sodium in the presence of benzophenone, and diethyl ether (ether) was dried over sodium–lead alloy and then over sodium wire. Dichloromethane, benzene, acetonitrile and 2–picolyl–lithium were distilled from calcium hydride, and triethylamine and di-isopropylamine were distilled from calcium hydride and stored over 3A molecular sieves. Other solvents and reagents were either purified by following the procedures outlined in *Purification of Laboratory Chemicals,*[1] or used in the form obtained from the chemical suppliers.

Chromatography.

Medium pressure (Flash) column chromatography was used in general for the purification of reaction mixtures. "Silica gel" refers to Amicon Matrex 84072 silica gel (230–400 mesh), or Merck 9385 silica gel. "Alumina" refers to Aldrich 19,997-4 neutral alumina. In addition, preparative centrifugally accelerated thin layer radial chromatography was employed for some separations, using a model 2 Chromatotron.

Thin layer chromatography (t.l.c.) was used extensively for following the course of reactions, for the analysis of fractions from chromatographic columns and for assessing the purity of compounds. It was performed on aluminium plates coated with kieselgel 60 F_{254} silica gel, and compounds were visualised in the first instance by illumination with short wavelength (254 nm) u.v. light. Thereafter visualisation was achieved using one of the following:

1. Aqueous potassium permanganate solution.

Spray/dip solution: 3 g Potassium permanganate, 20 g potassium carbonate dissolved in 5 cm^3 5% aqueous sodium hydroxide and 300 cm^3 water.

2. 2,4-Dinitrophenylhydrazine (DNP) for aldehydes and ketones.

Spray/dip solution: 12 g 2,4-DNP in 60 cm^3 conc. H_2SO_4 added to 80 cm^3 water and 200 cm^3 95% ethanol.

3. Dragendorff reagent (according to Munier and Macheboeuf) for alkaloids and other nitrogen-containing compounds.[2]

Solution a: 0.85 g bismuth (III) nitrate in 10 cm^3 glacial acetic acid and 40 cm^3 water.

Solution b: Dissolve 8 g potassium iodide in 20 cm^3 water.

Stock solution: Equal parts a and b, mixed.

Spray/dip solution: Stock solution (1 cm^3) mixed with glacial acetic acid (2 cm^3) and water (10 cm^3).

Retention factor (R_F) values are given for new compounds, particularly where more than one compound was present in the reaction mixture. These are quoted in the form (R_F *m*, solv. *n*) where *m*=numerical value of R_F and *n*=1,2,3,4 or 5, the latter refering to the five most commonly employed solvent systems for the elution of t.l.c. plates. Thus,

solv. 1 = Ethyl acetate-petrol (60- 80°C) (1:1).

solv. 2 = Ethyl acetate-petrol (60-80°C) (1:3).

solv. 3 = 1% Triethylamine in ethyl acetate.

solv. 4 = 0.4 M Ammonium chloride in methanol.

solv. 5 = 1% Ammonia (.880) in methanol-acetone-chloroform (2:3:10).

Other solvent systems used are quoted in full in the text.

Spectroscopy.

All physical data were recorded using the instruments at the University of Bath, and Organon SDG, Newhouse, Lanarkshire. Ultra violet (u.v.) spectra were recorded between 190–390 nm in 95% ethanol solution. The suffix "sh" refers to a shoulder or point of inflection. Infra red (i.r.) spectra were recorded and corrected with reference to the absorptions of polystyrene film. The appended letters (s, w, br) refer to the type of signal *i.e.* strong, weak, broad. Nuclear magnetic resonance (n.m.r.) spectra were recorded with TMS as an internal standard, and chemical shift values are quoted in parts per million downfield from TMS. The order of citation in parentheses is as follows: (i) number of equivalent nuclei (by integration), (ii) multiplicity (s, d, t, m *etc.*), (iii) coupling constant *e.g.* $J_{x,y}$ 5 Hz, (iv) assignment. Where hyperfine splitting occurs, multiplicities are given in the form "td" (triplet of doublets), "dm" (doublet of multiplets) *etc.* and the J values are quoted in the order: largest to smallest. Mass spectral data are given in the form: peak (relative intensity%), with the assignments (*e.g.* M^+) and type of ionisation specified.

Instrumentation.

m.p.	Electrothermal Mk II.
g.l.c.	Packard 429.
u.v.	Perkin-Elmer Lambda 3.
i.r.	Perkin-Elmer 197.
	Perkin-Elmer 938 G.
^{1}H n.m.r.	Jeol GX FT 400 (400 MHz).
	Jeol GX FT 270 (270 MHz).
	Bruker AM 200 (200 MHz).
	Varian EM-360 (60 MHz).

	Hitachi Perkin-Elmer R24 (60 MHz).
^{13}C n.m.r.	Jeol GX FT 270 (67.8 MHz).
m.s.	VG 7070E with 2000 data system.
Elemental.	Carlo Erba Elemental Analyser model 1106.

7.2 Experimental to Chapter 2.

Preparation of 1-(2-pyridyl)-3-buten-2-ol[3] *(56).*- Di-isopropylamine (1.8 cm^3, 12.8 mmol) was dissolved in dry THF (30 cm^3) under nitrogen and this was cooled to -10°C for 10 minutes. *n*-Butyl-lithium (7.36 cm^3 of a 1.6M solution in hexane) was added slowly dropwise to the stirred solution and after a further 10 minutes 2-picoline (1 cm^3, 10.7 mmol) was added. The mixture was stirred at room temperature for 1h to ensure the formation of 2-picolyl-lithium, and was then cooled to -10°C. A solution of acrolein (0.64 cm^2, 9.6 mmol) in dry THF (5 cm^3) was added dropwise, causing the dark red anion solution to become a clear pale yellow colour. After stirring for ½h, water (100 cm^3) was added and the mixture was extracted with chloroform (3 x 40 cm^3). The organic phase was washed with brine (2 x 20 cm^3), dried (Na_2SO_4) and concentrated to an oil. The crude oil was chromatographed on silica gel eluting with ethyl acetate-petrol (60-80°C) (1:2) to give the title compound (56) as an oil (R_F 0.35, solv. 1) which solidified on standing (770 mg, 54%), m.p. 38-39°C, (lit. 36°C) (Found: C, 72.2; H, 7.5: N. 9.3. Calc. for $C_9H_{11}NO$: C, 72.45; H, 7.4; N, 9.4%); $\nu_{max.}$ ($CHCl_3$) 3 300br (O-H), 2 930s (C-H), 2 460w, 1 980w, 1 950w, 1 915w, 1 850w, 1 590 (C=C), 1 570, 1 420br, 1 320, 1 150, 1 100br, 985, 920, 850 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 2.93 (1 H, dd. $J_{1,1(gem)}$ 15, $J_{1,2(vic)}$ 8 Hz, 1-H), 3.03 (2 H, dd, $J_{1,1(gem)}$ 15, $J_{1,2(vic)}$ 3.8 Hz, 1-H), 4.59 (1 H, m, 2-H), 5.11 [1 H, dt, $J_{3,4(cis)}$ 10.8, $J_{4,4(gem)}$, $J_{2,4(allylic)}$ 1.6 Hz, 4-H (Z)], 5.20 (1 H, br m, O*H*), 5.31 [1 H, dt, $J_{3,4(trans)}$ 17.3, $J_{4,4(gem)}$, $J_{2,4(allylic)}$ 1.6 Hz, 4-H (E)], 5.95 (1 H, ddd, $J_{3,4(trans)}$ 17.3, $J_{3,4(cis)}$

10.8, $J_{2,3}$ 5.4 Hz, 3 H), 7.16 (1 H, d, $J_{4',5'}$ 7.5 Hz, 5'-H), 7.18 (1 H, d, $J_{3',4'}$ 7.5 Hz, 3'-H), 7.63 (1 H, td, $J_{3',4',5'}$ 7.5, $J_{4',6'}$ 1.9 Hz, 4'-H), 8.50 (1 H, dm, $J_{5',6'}$ 4.9 Hz, 6'-H); δ_C (67.8 MHz; $CDCl_3$) 43.2 (t, 1-C), 71.9 (d, 2-C), 114.6 (t, 4-C), 121.5 (d, 5'-C), 123.7 (d, 3'-C), 136.7 (d, 4'-C), 140.1 (d, 3-C), 148.5 (d, 6'-C), 159.5 (s, 2'-C); *m/z* (isobutane CI) 150 (*M+1*, 100%), 132 (58, $M - H_2O$), 93 (25).

Attempted preparation of 1-(2-pyridyl)-3-buten-2-one (53) via *Oppenauer oxidation of the alcohol*[3] *(56).*- The alcohol (56) (50 mg, 0.34mmol) was dissolved in dry acetone (30 cm^3) and to this was added aluminium isopropoxide (70 mg, 0.34 mmol). The mixture was heated under reflux for 12h, allowed to cool, and the solution filtered and concentrated to an oil. Analysis by t.l.c. and ^1H n.m.r. indicated the presence of starting alcohol with traces of base line decomposition products. The experiment was repeated several times, varying the reaction conditions in each case [increased period of reflux; changing the solvent to MEK; performing the experiment on 5 g of alcohol and 7 g of aluminium isopropoxide precisely as quoted in the literature, assuming a poor yield]. No compound corresponding to the desired product was ever isolated.

Other attempted oxidation procedures.- Reagents were either used as available commercially or prepared according to the appropriate literature method. Thus, γ-active manganese dioxide was prepared and used according to the method of Attenburrow.[4] PCC was used as directed by Corey,[5] PDC was used according to the method of Coates,6 whilst Fetizon's reagent (Ag_2CO_3 on celite) was prepared and used as outlined by Fieser.[7] A stock solution of Jones reagent was prepared as follows: chromium trioxide (1.27 g) was dissolved in H_2SO_4 (2 cm^3) and water (6 cm^3). The required amount of reagent was then used with acetone employed as the reaction solvent. Pfitzner and Moffatt DMSO/DCC oxidations were carried out as rec-

commended by the authors[8] and the Swern oxidation attempted employed DMSO and trifluoroacetic anhydride at -65°C.[9]

Attempted preparation of the enone (53) via Moffatt oxidation of the alcohol (56).- The alcohol (56) (100 mg, 0.67 mmol) was dissolved in dry DMSO (1.5 cm^3) and to this was added dry acetic anhydride (1 cm^3). The solution was stirred overnight at room temperature and after this time t.l.c. showed complete conversion of starting material to a new compound of slightly higher R_F. The reaction mixture was poured into water (20 cm^3), stirred until homogeneous and extracted with ethyl acetate (3 × 10 cm^3). The organic phase was then washed with sodium hydrogen carbonate solution (2 × 5 cm^3) and brine (3 × 5 cm^3), dried (Na_2SO_4) and concentrated to afford *1-(2-pyridyl)-3-buten-2-ol acetate* (57) (R_F 0.45, solv. 1) as an oil (10 mg, 8%), $\nu_{max.}$ ($CHCl_3$) 2 920 (C-H), 1 720 (C=O), 1 590 (C=C), 1 570 cm^{-1}; δ_H (60 MHz; $CDCl_3$) 2.00 (3 H, s, C*H*$_3$), 3.10 (2 H, d, $J_{1,2}$ 7 Hz, 1-H), 5.20 (2 H, m, 4-H), 5.65 (2 H, m, 2-H, 3-H), 7.15 (2 H, m, 3'-H, 5'-H), 7.60 (1 H, td, $J_{3',4',5'}$ 7, $J_{4',6'}$ 2 Hz, 4' H), 8.50 (1 H, dm, $J_{5',6'}$ 5 Hz, 6' H); *m/z* (isobutane CI) 192 (*M*+*1*, 35%), 148 (28), 132 (100), 130 (29).

Attempted preparation of the enone (53) via *the reaction between 2-picolyl-lithium and lithium acrylate.*- Di-isopropylamine (1.8 cm^3, 12.8 mmol) was dissolved in dry THF (30 cm^3) under nitrogen and this was cooled to -10°C for 10 minutes. *n*-Butyl-lithium (7.36 cm^3 of a 1.6M solution in hexane) was added slowly dropwise to the stirred solution and after a further 10 minutes 2-picoline (1 cm^3, 10.7 mmol) was added. The mixture was stirred at room temperature for 1h to ensure the formation of 2-picolyl-lithium, and was then cooled to -10°C. Acrylic acid (0.73 cm^3, 10.7 mmol) was dissolved in dry THF (10 cm^3) and this was stirred at -5°C whilst *n*-butyl-lithium (7.36 cm^3 of a 1.6M solution in hexane) was added. The lithium salt

formed as a semi-soluble white precipitate. Into this solution was dripped the 2-picolyl-lithium solution *via* a cannula and the mixture was stirred at room temperature overnight. Analysis by t.l.c. indicated that starting materials were still present, and so TMEDA (5 cm^3) was added and the mixture was heated under reflux for several hours. Since there still appeared to be no discernable products after this time the experiment was abandoned.

Attempted preparation of the enone (53) via *the reaction between 2-picolyl-lithium and acrylonitrile.*- Di-isopropylamine (1.8 cm^3, 12.8 mmol) was dissolved in dry THF (30 cm^3) under nitrogen and this was cooled to -10°C for 10 minutes. *n*-Butyl-lithium (7.36 cm^3 of a 1.6M solution in hexane) was added slowly dropwise to the stirred solution and after a further 10 minutes 2-picoline (1 cm^3, 10.7 mmol) was added. The mixture was stirred at room temperature for 1h to ensure the formation of 2-picolyl-lithium, and was then cooled to -10°C. Acrylonitrile (0.63 cm^3) was added dropwise and the mixture was stirred at room temperature. Analysis by t.l.c. taken at intervals indicated the presence of starting materials, and overnight stirring followed by the usual work-up procedure resulted in the isolation of a complex mixture. The experiment was therefore abandoned.

Attempted preparation of the enone (53) via *the reaction between 2-picolyl-lithium and methyl acrylate.*- Di-isopropylamine (1.8 cm^3, 12.8 mmol) was dissolved in dry THF (30 cm^3) under nitrogen and this was cooled to -10°C for 10 minutes. *n*-Butyl-lithium (7.36 cm^3 of a 1.6M solution in hexane) was added slowly dropwise to the stirred solution and after a further 10 minutes 2-picoline (1 cm^3, 10.7 mmol) was added. The mixture was stirred at room temperature for 1h to ensure the formation of 2-picolyl-lithium, and was then cooled to -10°C. This was added dropwise *via* a cannula to a stirred solution of methyl acrylate (0.48 cm^3, 5.35 mmol) in

dry THF (10 cm^3) at -10°C. The dark red colour of the anion was lost and a clear yellow solution formed. After stirring for 1h at room temperature, water (50 cm^3) was added and the mixture extracted with chloroform (3 × 30 cm^3), the organic phase washed with brine (2 × 20 cm^3), dried (Na_2SO_4) and concentrated to an oil. The crude mixture was chromatographed on silica gel with ethyl acetate–petrol (60–80°C) (1:1) as the eluant to yield *1-di-(2-picolyl)-2-propen-1-ol* (58) as an oil (180 mg, 14%)(R_F 0.35, solv. 1), $\nu_{max.}$ ($CHCl_3$) 3 300br (O–H), 2 920s (C–H), 2 470w, 1 980w, 1 950w, 1 915w, 1 850w, 1 720w, 1 590s (C=C), 1 570, 1 420br, 1 150, 1 120, 1 100, 995, 910 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 3.05 [4 H, s, ($CH_2Py)_2$], 4.90 [1 H, dd, J_{cis} 10.5, J_{gem} 1.5 Hz, 4–H (Z)], 5.14 [1 H, dd, J_{trans} 17, J_{gem} 1.5 Hz, 4–H (E)], 5.87 (1 H, dd, J_{trans} 17, J_{cis} 10.5 Hz, 3–H], 7.10–7.30 (1 H, br s, O*H*), 7.12 (2 H, dd, $J_{4',5'}$ 7.5, $J_{5',6'}$ 5.25 Hz, 5'–H), 7.24 (2 H, d, $J_{3',4'}$ 7.5 Hz, 3'–H), 7.59 (2 H, td, $J_{3',4'5'}$ 7.5, $J_{4',6'}$ 1.5 Hz, 4'–H), 8.46 (2 H, dm, $J_{5',6'}$ 5.25 Hz, 6'–H); δ_C (67.8 MHz; $CDCl_3$) 47.3 [t, (italic$CH_2Py)_2$], 75.5 (s, 2–C), 113.3 (t, 4–C), 121.3 (d, 5'–C), 125.0 (d, 3'–C), 136.2 (d, 4'–C), 143.0 (d, 3–C), 148.1 (d, 6'–C), 158.6 (s, 2'–C); *m/z* (isobutane CI) 241 (*M+1*, 100%), 223 (28. *M* − H_2O), 148 (88), 94 (67), 93 (23).

Attempted preparation of the enone (59) via *the reaction between 2-picolylcopper and acryloyl chloride.*– Methyl-lithium (13.3 cm^3 of a 1.5M solution in Et_2O) was dissolved in dry THF (100 cm^3) in a stirred 3–neck dropping funnel under nitrogen. The solution was cooled to –10°C and 2–picoline (1.97 cm^3, 20 mmol) was added. This was allowed to warm to room temperature over 1h and then cooled to –78°C. Copper (I) iodide (7.6 g, 40 mmol) was added to the solution and this was stirred at about –60°C for 1h. The 2–picolylcopper solution was added to a solution of acryloyl chloride (1.62 cm^3) in THF (50 cm^3) at –60°C with vigorous stirring. The mixture was allowed to warm to 0°C over 2h and after this time water (80 cm^3) was added. The THF was removed *in vacuo* and the resulting suspension was extracted

several times with ethyl acetate. The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated to an oil. This was chromatographed on silica gel with ethyl acetate–petrol (60–80)°C (1:9) as eluant to yield an oil (52 mg). This compound exhibited complex spectra which made structural elucidation extremely difficult. Further attempts to purify the product failed and the experiment was therefore abandoned.

Attempted preparation of the enone (58) via *the reaction between 2-picolyl-lithium and acryloyl chloride.* - Methyl-lithium (7.5 cm^3 of a 1.5M solution in Et_2O) was dissolved in dry THF (100 cm^3) in a stirred 3-neck dropping funnel under nitrogen. The solution was cooled to -10°C and 2-picoline (1 cm^3, 10 mmol) was added. This was allowed to warm to room temperature over 1h and then cooled to -78°C. The 2-picolyl-lithium solution was added dropwise over ½h to a vigorously stirred solution of of acryloyl chloride (0.81 cm^3, 10 mmol) in dry ether (100 cm^3) at -78°C. When the addition was complete, the reaction mixture was allowed to warm to 0°C, and after a further 20 minutes 2M HCl (20 cm^3) was added to afford a clear yellow biphasic mixture. This was extracted several times with 5M HCl and the combined acidic extracts were basified carefully with 10M KOH until just acid, and then made just basic with anhydrous potassium carbonate. The basic solution was extracted several times with ethyl acetate, the combined organic phases were dried (Na_2SO_4), and concentrated to afford an oil. This was chromatographed on silica gel with ethyl acetate–petrol (60–80°C) (1:4) as the eluant to yield *2-picolinyl acrylate* (62) (R_F 0.50, solv. 1) as a clear oil (95 mg, 6.5%); $\nu_{max.}$ (CH_2Cl_2) 3 020w (aromatic C–H), 2 930 (aliphatic C–H), 1 725vs (C=O), 1 595 (C=C), 1 572, 1 474, 1 406s, 1 295, 1 184vs, 1 068, 985, 808 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 5.33 (2 H, s, CH_2=CHCO$_2$C*H*$_2$Py), 5.90 [1 H, dd, J_{cis} 10, J_{gem} 1 Hz, C*H*$_2$(Z)=CHCO$_2$CH$_2$Py], 6.24 (1 H, dd, J_{trans} 17.5, J_{cis} 10 Hz, CH_2=C*H* CO$_2$CH$_2$Py), 6.52 [1 H, dd, J_{trans}

17.5, J_{gem} 1 Hz, CH_2(E)=$CHCO_2CH_2Py$], 7.26 (1 H, dd, $J_{4,5}$ 7.5, $J_{5,6}$ 1 Hz, 5'-H), 7.37 (1 H, $J_{3,5}$ 7.5 Hz, 3'-H), 7.70 (1 H, td, $J_{3,4,5}$ 7.5, $J_{4,6}$ 2.5 Hz, 4'-H), 8.60 (1 H, dm, $J_{5,6}$ 5 Hz, 6'-H); δ_C (67.8 MHz; $CDCl_3$) 66.8 (t, CH_2=$CHCO_2C$ H_2Py), 121.7 (d, 5'-C), 122.8 (d, 3'-C), 127.9 (d, CH_2=C HCO_2CH_2Py), 131.4 (t, C H_2=$CHCO_2CH_2Py$), 136.7 (d, 4'-C), 149.4 (d, 6'-C), 155.6 (s, 2'-C), 165.7 (s, CH_2=CHC O_2CH_2Py); *m/z* (isobutane CI) 164 (*M+1*, 100%), 108 (28) (Found: M^+, 163.0637. $C_9H_9NO_2$ requires *M*, 163.0632).

Attempted preparation of the ynone (54) via *the reaction between 2-picolyl-lithium and methyl propiolate.*- Di isopropylamine (0.18 cm^3,1.3 mmol) was dissolved in dry THF (10 cm^3) under nitrogen and this was cooled to -10°C for 10 minutes. *n*-Butyl-lithium (0.74 cm^3 of a 1.6M solution in hexane) was added slowly dropwise to the stirred solution and after a further 10 minutes 2-picoline (0.1 cm^3, 1 mmol) was added.The mixture was stirred at room temperature for 1h to ensure the formation of 2-picolyl-lithium. Methyl propiolate (0.1 cm^3, 1 mmol) was dissolved in THF (3 cm^3) and cooled to -65°C. To this was added *n*-butyl-lithium (0.73 cm^3 of a 1.6M solution in hexane) keeping the temperature below -65°C. The solution was stirred at the same temperature for 10 minutes after the addition and the cooled (-60°C) solution of 2-picolyl-lithium was added dropwise *via* a cannula. The mixture was stirred for ½h at -65°C and then allowed to warm to room temperature. The solution was quenched with water (5 cm^3), extracted with chloroform (3 × 10 cm^3), washed with brine (2 × 5 cm^3), dried (Na_2SO_4) and concentrated to an oil. This was chromatographed on silica gel eluting with ethyl acetate-petrol (60-80°C) (1:1) to yield *1-di-(2-picolyl)-2-propyn-1-ol* (65) (R_F 0.15, solv. 1) as an oil, (10 mg, 4.2%), $\nu_{max.}$ ($CHCl_3$) 3 320s (alkyne C-H), 3 300br (O-H), 2 950 (C-H), 1 600s (C=C), 1 585, 1 430br, 1 160, 1 115s, 1 050br, 1 010w, 920 cm^{-1}; δ_H (60 MHz; CCl_4) 1.2-1.5 (1 H, br s, OH), 2.30 (1 H, s, C≡CH), 3.30 [4 H, s, HC≡CCOH(CH_2Py)$_2$], 7.40 (6 H,

m, 3', 4', and 5' H), 8.60 (2 H, dm, 6' H); *m/z* (isobutane CI) 239 (*M*+*1*, 32%), 223 (60), 222 (40), 221 (82, $M - H_2O$), 146 (47), 94 (92).

Attempted preparation of the ynone (54) via *the reaction between 2-picolyl-lithium and propiolic acid chloride.*- Di-isopropylamine (0.9 cm^3, 6.4 mmol) was dissolved in dry THF (30 cm^3) under nitrogen and this was cooled to -10°C for 10 minutes. *n*-Butyl-lithium (3.7 cm^3 of a 1.6M solution in hexane) was added slowly dropwise to the stirred solution and after a further 10 minutes 2-picoline (0.5 cm^3, 5.4 mmol) was added. The mixture was stirred at room temperature for 1h to ensure formation of the 2-picolyl-lithium, and then cooled to -78°C. The anion solution was added to a solution of propiolic acid chloride (1 cm^3) which had been prepared according to the method of Balfour [10] in THF (10 cm^3) at -78°C. The normal work-up procedure resulted in an inseparable mixture; the experiment was therefore abandoned.

Preparation of propynal[11] *(69)- 1.*- A solution of chromium trioxide (30 g) in sulphuric acid (20 cm^3) and water (60 cm^3) was added dropwise with stirring over 1h to a solution of propyn-1-ol (1.87 cm^3) in MEK (10 cm^3). The reaction temperature was kept at 20-25°C during the addition and the viscous mixture was stirred for 5h. Water (20 cm^3) was added, the organic phase was extracted with diethyl ether (3 × 50 cm^3), washed with brine (4 × 10 cm^3), and water (10 cm^3), and dried ($MgSO_4$). The mixture was distilled at atmospheric pressure to give two fractions boiling at 34°C (mainly diethyl ether) and two boiling at 55°C (a mixture of MEK and propynal). The ^1H n.m.r. spectrum (60 MHz) exhibited a peak at δ_H 9.20 corresponding to the resonance of the propynal aldehyde proton.

Attempted preparation of the alkynol (68) via *the reaction between 2-picolyl-*

lithium and the propynal/MEK mixture.- Di-isopropylamine (0.9 cm^3, 6.4 mmol) was dissolved in dry THF (30 cm^3) under nitrogen and this was cooled to -10°C for 10 minutes. *n*-Butyl-lithium (3.7 cm^3 of a 1.6M solution in hexane) was added slowly dropwise to the stirred solution and after a further 10 minutes 2-picoline (0.5 cm^3, 5.4 mmol) was added. The mixture was stirred at room temperature for 1h to ensure the formation of 2-picolyl-lithium. The propynal/MEK mixture (2 cm^3) was dissolved in THF (10 cm^3) and added to the 2-picolyl-lithium solution at -78°C which turned from dark red to yellow. After stirring for 1h at room temperature water (25 cm^3) was added, the mixture was extracted with chloroform (3 × 30 cm^3), washed with brine (2 × 10 cm^3), dried (Na_2SO_4) and concentrated to an oil. The crude material was chromatographed on silica gel eluting with ethyl acetate-petrol (60-80°C) (3:7) to afford *1-(2-pyridyl)-2-methylbutan-2-ol* (70) (R_F 0.50, solv. 1) as an oil (150 mg, 23%), $\nu_{max.}$ ($CHCl_3$) 3 300br, vs (O-H), 2 920vs (C-H), 1 700w, 1 590 (C=C), 1 570, 1 420br, 1 370, 1 325w, 1 140, 1 115, 1 085, 995, 930, 865 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 0.93 (3 H, t, $J_{3,4}$ 7.5 Hz, 4-H), 1.14 (3 H, s, 2-Me), 1.50 (2 H, qd, $J_{3,4}$ 7.5, $J_{3,OH}$ 1.5 Hz, 3-H), 2.85 (1 H, d, $J_{1,1(gem)}$ 14.3 Hz, 1-H), 2.96 (1 H, d, $J_{1,1(gem)}$ 14.3 Hz, 1-H), 5.40-6.00 (1 H, br s, *OH*), 7.14 (1 H, d, $J_{3',4'}$ 7.5 Hz, 3'-H), 7.17 (1 H, dd, $J_{4',5'}$ 7.5, $J_{5',6'}$ 5.25 Hz, 5'-H), 7.64 (1 H, td, $J_{3',4',5'}$ 7.5, $J_{4',6'}$ 2 Hz, 4'-H), 8.50 (1 H, dm, $J_{5',6'}$ 5.25 Hz, 6'-H); δ_C (67.8 MHz; $CDCl_3$) 8.5 (q, 4-C), 26.3 (q, 2-Me), 34.7 (t, 3-C), 46.4 (t, 1-C), 72.8 (s, 2-C), 121.3 (d, 5'-C), 124.4 (d, 3'-C), 136.7 (d, 4'-C), 148.3 (d, 6'-C), 160.0 (s, 2'-C); *m/z* (isobutane CI) 166 (*M* + *1*, 100%), 153 (31), 148 (56, $M - H_2O$), 94 (30), 73 (25).

Preparation of propynal (69)[12] *(69)- 2.*- A 500 cm^3 round bottomed flask was fitted with a thermometer, a 100 cm^3 pressure equalising dropping funnel, an over-head stirrer and a fine capillary tube for introducing nitrogen near the bottom of the flask. A fifth outlet was for an exit tube attached to three traps in series connected to

a water pump *via* a manometer. In the flask was placed 1-propynol (30 cm^3) and a cooled (ice/salt bath) solution of sulphuric acid (33.75 cm^3) in water (50 cm^3). The last two traps in series were cooled to -78°C using liquid nitrogen and the first trap was cooled to about -15°C. The pressure in the system was reduced to 40–60 mm Hg, nitrogen was introduced through the capillary and the mixture was stirred vigorously. A solution of chromium trioxide (52.5 g) in water (100 cm^3) and sulphuric acid (33.75 cm^3) was added dropwise over 3h maintaining the temperature between 2–10°C. After the addition was complete, the ice/salt bath was removed and the flask allowed to warm to room temperature whilst the pressure was gradually lowered to 14–20 mm Hg to remove the last of the aldehyde. The condensates of traps 2 and 3 were combined and dried over sodium sulphate. The first trap contained a large amount of water and so brine was added, the propynal separated in a funnel and dried over sodium sulphate. The combined propynal, yield (3 g, 12.5%), was used in reactions without further purification.

Preparation of the alkynol (68).- Di-isopropylamine (0.9 cm^3, 6.4 mmol) was dissolved in dry THF (30 cm^3) under nitrogen and this was cooled to -10°C for 10 minutes. *n*-Butyl-lithium (3.7 cm^3 of a 1.6M solution in hexane) was added slowly dropwise to the stirred solution and after a further 10 minutes 2-picoline (0.5 cm^3, 5.4 mmol) was added. The mixture was stirred at room temperature for 1h to ensure formation of the 2-picolyl-lithium, and then cooled to -78°C. A solution of propynal (0.3 cm^3, 5.4 mmol) in THF (5 cm^3) was added slowly dropwise to the stirred anion solution which changed colour from dark red to light brown. The mixture was allowed to warm to room temperature and after 20 minutes water was added (20 cm^3). Most of the THF was removed *in vacuo* and the organic phase was extracted with chloroform (3 × 20 cm^3). The combined organic extracts were washed with brine (2 × 15 cm^3), dried (Na_2SO_4), and concentrated to afford an oil. This was

chromatographed on silica gel using 20%-50% ethyl acetate in petrol (60–80°C) as the eluant to yield *1-(2-pyridyl)-3-butyn-2-ol (68)* (R_F 0.30, solv. 1) as an amorphous solid (350 mg, 44%) (Found: C, 73.2; H, 6.3; N, 9.3. C_9H_9NO requires C, 73.45; H, 6.2; N, 9.5%); $\nu_{max.}$ (nujol) 3 300 (alkyne C–H), 3 050br (O–H), 2 100w (C≡C), 1 590 (C=C), 1 565, 1 320w, 1 290w, 1 170w, 1 150w, 1 090w, 1 060s, 1 020, 1 000, 755 cm^{-1}; δ_H (60 MHz; $CDCl_3$) 2.40 (1 H, d, $J_{2,4}$ 2 Hz, 4–H), 3.20 (2 H, d, $J_{1,2}$ 6 Hz, 1–H), 4.90 (1 H, td, $J_{1,2}$ 6, $J_{2,4}$ 2 Hz, 2–H), 5.60-5.80 (1 H, br s, O*H*), 7.30 (2 H, m, 3'–H, 5'–H), 7.65 (1 H, m, 4'–H), 8.45 (1 H, dm, $J_{5',6'}$ 5 Hz, 6'–H); *m/z* (isobutane CI) 148 (*M+1*, 100%), 130 (21, $M - H_2O$).

7.3 Experimental to Chapter 3.

Preparation of the enyne (48).– The alkynol (68) (30 mg, 0.2 mmol) was dissolved in dry dichloromethane (5 cm^3) under nitrogen and triethylamine (0.3 cm^3, 2 mmol) was added. The stirred solution was cooled to -5°C and methanesulphonyl chloride (0.017 cm^3, 0.22 mmol) was added dropwise. The cooling bath was removed and after the mixture had warmed to room temperature it was heated under reflux for ½h. Analysis by t.l.c. at this stage indicated formation of the mesylate, and DBU (0.1 cm^3, 0.6 mmol) was added. The mixture was heated for a further 1h at reflux by which time analysis by t.l.c. showed formation of the elimination product. The solvents were removed *in vacuo* and the crude mixture chromatographed on silica gel with ethyl acetate–petrol (60–80°C) (1:3) as the eluant. *1-(2-Pyridyl)but-1-en-3-yne (48)* (R_F 0.65, solv. 2) was isolated as an oil (26 mg, 99%), $\nu_{max.}$ ($CHCl_3$) 3 300vs (alkyne C–H), 2 950 (C–H), 1 580, 1 560 (C=C), 1 460, 1 420, 1 145w, 1 090w, 990w, 950vs cm^{-1}; δ_H (270 MHz; $CDCl_3$) 3.15 (1 H, dd, $J_{2,4}$ 2.7, $J_{1,4}$ 0.7 Hz, 4–H), 6.73 (1 H, dd. $J_{1,2}$ 16. $J_{2,4}$ 2.7 Hz, 2–H), 7.06 (1 H, d, $J_{1,2}$ 16 Hz, 1–H), 7.18 (1 H, ddd, $J_{4',5'}$ 7.4, $J_{5',6'}$ 4.7, $J_{3',5'}$ 1.4 Hz, 5'–H), 7.23 (1 H, d, $J_{3',4'}$ 7.4 Hz, 3'–H), 7.64 (1 H, td, $J_{3',4',5'}$ 7.4,

$J_{4',6'}$ 2 Hz, 4'-H), 8.56 (1 H, d, $J_{5',6'}$ 4.7 Hz, 6'-H); δ_C (67.8 MHz; $CDCl_3$) 81.1 (d, 4-C), 82.5 (s, 3-C), 111.4 (d, 2-C), 122.3 (d, 5'-C), 123.2 (d, 3'-C), 136.6 (d, 4'-C), 141.8 (d, 1-C), 149.7 (d, 6'-C), 153.6 (s, 2'-C); *m/z* (low eV EI) 129 (M^+, 54%), 94 (52) (Found: M^+, 129.058. C_9H_7N requires M, 129.0577).

Attempted reaction of ethyl diazoacetate and the enyne (48).- The enyne (48) (26 mg, 0.2 mmol) and ethyl diazoacetate (23 mg, 0.2 mmol) were dissolved in dry benzene (20 cm^3) and this was heated under reflux for 3 days. Analysis of the reaction by t.l.c. during this time indicated the presence of starting materials only, work-up led to the isolation of base line decomposition products; the experiment was therefore abandoned.

Preparation of 5-N,N-dimethylamino-1,3,4-oxathiazol-2-one (72).[13] *(72).*- 1,1-Dimethylurea (2.5 g, 28 mmol) was dissolved in dry acetonitrile (20 cm^3) under nitrogen. To the stirred solution was added dropwise a solution of chlorocarbonylsulphenylchloride (0.74 cm^3, 9 mmol) in acetonitrile (2 cm^3). The reaction mixture was stirred for 1h and methanol (5 cm^3) was added to decompose any remaining reagent. The solvents were removed *in vacuo* and dichloromethane (10 cm^3) was added. The precipitate was removed and the filtrate was chromatographed on silica gel with dichloromethane-petrol (60-80°C) (3:1) as eluant to yield the title compound as a colourless gum (240 mg, 19%); $\nu_{max.}$ ($CHCl_3$) 1 715s (C=O), 1 650s (C=C), 2 910w (C-H), 1 420s, 1 360s cm^{-1}; δ_H (60 MHz; $CDCl_3$) 3.2 [6 H, s, $N(CH_3)_2$]; *m/z* (low eV EI) 146 (M^+, 100%), 89 (72), 61 (26).

Attempted addition of N,N-dimethylaminonitrile sulphide to the enyne (48).- The enyne (100 mg, 0.78 mmol) was dissolved in dry, distilled DMF (4 cm^3) under nitrogen. The mixture was heated to 140°C with stirring and a solution of 5-

N,N-dimethylamino-1,3,4-oxathiazol-2-one (72) (125 mg, 0.86 mmol) in DMF (1 cm^3) was added dropwise with stirring to the reaction mixture. Heating was continued for ½h and once the reaction had cooled, the solvents were removed *in vacuo*. The residue was chromatographed on silica gel with ethyl acetate–petrol (60–80°C) (1:3) as eluant to yield recovered enyne (43 mg) only; thus the experiment was abandoned.

Preparation of benzaldehyde oxime[14] *(79).*- To a solution of benzaldehyde (5.31 g) in water (12.5 cm^3), ethanol (12.5 cm^3) and ice (21.5 cm^3) was added hydroxyammonium chloride (3.82 g). Sodium hydroxide (5.25g) as a 50% solution in water was added with stirring, keeping the temperature at 25–30°C by adding ice. The mixture was stirred for 1h, extracted with diethyl ether (50 cm^3) to remove neutral impurities, acidified carefully dropwise with c.HCl to pH 6 with ice bath cooling and extracted with diethyl ether (2 x 50 cm^3). The combined extracts were dried (Na_2SO_4), concentrated to an oil (4.69g, 78%), and used in this form without further purification, δ_H (60 MHz; CCl_4) 7.45 (5 H, m, Ph), 8.25 (1 H, s, PhC*H*=NOH), 9.65 (1 H, br s, O*H*); *m/z* (70 eV EI) 121 (M^+, 100), 78 (68), 77 (61), 66 (24), 51 (42).

Preparation of benzohydroximinoyl chloride (74).- Benzaldehyde oxime (73) (0.55 g, 4.5 mmol) was dissolved in chloroform (30 cm^3) and this was cooled to -30°C with stirring. Chlorine gas was gently bubbled through the solution for ½h keeping the temperature at -30°C. The solution was then stirred at -30°C for a further ½h, without further addition of chlorine, the colour of the solution having changed from blue-green to grass-green. The excess chlorine and solvents were removed *in vacuo* and the resulting oil was used without further purification (0.77 g, 100%), δ_H (60 MHz; $CDCl_3$) 7.35 (3 H, m, 3', 4' and 5'-H), 7.75 (2 H, m, 2'-H, 6'-H), 9.10 (1 H, s, O*H*); *m/z* (low eV EI) 157 [M^+ (^{37}Cl), 18%], 155 [M^+ (^{35}Cl), 59], 120 (30, M – Cl),

119 (100, M − Cl).[14]

Preparation of the 3-phenylisoxazole (76).- The enyne (48) (36 mg, 0.28 mmol) was dissolved in dry diethyl ether (20 cm^3) under nitrogen and to this was added benzohydroximinoyl chloride (43 mg, 0.28 mmol). A solution of triethylamine (0.043 cm^3, 0.31 mmol) in dry diethyl ether (20 cm^3) was added dropwise to the stirred mixture at room temperature over 3h. Water (15 cm^3) was added to the mixture, which had precipitated triethylamine hydrochloride, and the organic phase was separated. The aqueous layer was extracted twice with diethyl ether and the combined organic phases were dried (Na_2SO_4) and concentrated to an oil. This was chromatographed on silica gel using ethyl acetate-petrol (60-80°C) (1:3) as the eluant to yield *(E)-5-[2-(2-pyridyl)ethenyl]-3-phenylisoxazole (76)* (R_F 0.25, solv. 2) as a solid (30 mg, 43%), m.p. 98-100°C (Found: C, 77.8; H, 4.7; N, 11.2. $C_{16}H_{12}N_2O$ requires C, 77.4; H, 4.9; N, 11.3%); $\lambda_{max.}$ (EtOH) 200 (ϵ 35 400 $dm^3\ mol^{-1}\ cm^{-1}$), 244 (16 115), 277sh (15 840), 312 (33 380), 325sh nm (14 200); $\nu_{max.}$ ($CHCl_3$) 2 950 (C-H), 1 580s, 1 555 (C=C) 1 460, 1 430, 1 400, 1 145w, 1 090w, 990w, 965s, 950 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 6.65 (1 H, s, 4-H), 7.25 (1 H, ddd, $J_{4'',5''}$ 8, $J_{5'',6''}$ 5, $J_{3'',5''}$ 1.5 Hz, 5''-H), 7.40 (1 H, d, $J_{3'',4''}$ 8 Hz, 3''-H), 7.42 (1 H, d, $J_{1',2'}$ 16 Hz, 1'-H), 7.48 (3 H, m, 3, 4 and 5-H Ph), 7.63 (1 H. d, $J_{1',2'}$ 16 Hz, 2'-H), 7.72 (1 H, td, $J_{3'',4'',5''}$ 8, $J_{4'',6''}$ 2 Hz, 4''-H), 7.85 (2 H, m, 2 and 6 H Ph), 8.65 (1 H, dm, $J_{5'',6''}$ 5 Hz, 6''-H); m/z (low eV EI) 248 (M^+, 100%), 145 (30) (Found: M^+, 248.0944. $C_{16}H_{12}N_2O$ requires M, 248.0949).

Preparation of ethyl chloro-oximidoacetate[15] *(79).*- Glycine ethyl ester hydrochloride (6.97 g, 5 mmol) was dissolved in water (9.5 cm^3) and the solution was cooled to -5°C with stirring. To this solution was added HCl (4.15 cm^3) and a solution of sodium nitrite (3.44 g, 5 mmol) in water (5 cm^3) was added dropwise causing

the evolution of nitrogen and nitric oxide. A further equivalent of HCl (4.15 cm^3) was added, followed by sodium nitrite (3.44 g, 5 mmol) in water (5 cm^3). The product separated from the aqueous solution as a yellowish solid after a few minutes. The cold mixture was filtered with suction, dissolved in hot benzene, filtered and concentrated to a small liquid volume. Hot petrol (60-80°C) was added and the product crystallised on cooling as a colourless solid, m.p. 79°C (lit[15] 80°C (Found: C, 31.5; H, 4.0; N, 9.1. Calc. for $C_4H_6O_3NCl$: C, 31.7; H, 3.95; N, 9.24%); *m/z* (isobutane CI) 154 [*M+1* (^{37}Cl), 33%], 152 [*M+1* (^{35}Cl), 100], 124 (33), 116 (90, *M* − HCl).

Preparation of the isoxazole (45).- The enyne (48) (36 mg, 0.28 mmol) and ethyl chloro-oximidoacetate (63 mg, 0.42mmol) were dissolved in dry diethyl ether (20 cm^3) and stirred at room temperature under nitrogen. A solution of triethylamine (0.06 cm^3, 0.42 mmol) in dry diethyl ether (20 cm^3) was added dropwise over 1h to the vigorously stirred reaction mixture, causing precipitation of triethylamine hydrochloride. After stirring for a further ½h water (15 cm^3) was added and the organic layer was separated. The aqueous phase was extracted with diethyl ether (2 x 10 cm^3), the combined organic extracts were dried (Na_2SO_4) and concentrated to afford an oil. This was chromatographed on silica gel with ethyl acetate-petrol (60-80°) (1:3) as eluant to yield *ethyl 5-[2-(2-pyridyl)ethenyl]isoxazole-3-carboxylate (45)* (R_F 0.65, solv. 1) as a colourless crystalline solid (30 mg, 44%), m.p. 83-84°C (from ethanol) (Found: C, 64.2; H, 4.95; N, 11.4. $C_{13}H_{12}N_2O_3$ requires C, 63.9; H, 4.95; N, 11.5%); $\lambda_{max.}$ (EtOH) 209 (ϵ 7 970 $dm^3\ mol^{-1}\ cm^{-1}$), 273sh (10 740), 311 nm (24 670); $\nu_{max.}$ ($CHCl_3$) 1 730s (C=O), 1 585 (C=C), 1 445, 1 285, 1 100, 1 010w, 990w, 970 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.44 (3 H, t, *J* 6.75 Hz, $CO_2CH_2CH_3$), 4.46 (2 H, q, *J* 6.75 Hz, $CO_2CH_2CH_3$), 6.74 (1 H, s, 4-H), 7.25 (1 H, ddd, $J_{4',5'}$ 8, $J_{5',6'}$ 4.5, $J_{3',5'}$ 1 Hz, 5'-H), 7.39 (1 H, d, $J_{3',4'}$ 8 Hz, 3'-H), 7.41 (1 H, d, $J_{1',2'}$ 16 Hz, 1'-H), 7.60 (1 H, d, $J_{1',2'}$ 16 Hz, 2'-H), 7.72 (1 H, td, $J_{3',4',5'}$ 8, $J_{4',6'}$ 1.7 Hz, 4'-H), 8.65 (1 H, dm,

$J_{5',6'}$ 4.5 Hz, 6''-H); δ_C (67.8 MHz; $CDCl_3$) 14.1 (q, $CO_2CH_2\underline{C}H_3$), 62.1 (t, $CO_2\underline{C}H_2CH_3$), 103.1 (d, 4-C), 115.8 (d, 1'-C), 123.6 (d, 5''-C), 123.9 (d, 3''-C), 134.4 (d, 2'-C), 136.8 (d, 4''-C), 149.9 (d, 6''-C), 153.0 (s, 2''-C), 156.7 (s, 5-C), 159.8 (s, 3-C), 169.6 (s, $\underline{C}O_2Et$); *m/z* (low eV EI) 244 (M^+, 100%), 171 (12, $M - CO_2Et$), 145 (65).

Preparation of 1-(2-pyridyl)buta-1,3-diene (50).- The alcohol (56) (10 g, 67mmol) was dissolved in dry dichloromethane (250 cm^3) with stirring under nitrogen. Triethylamine (17 cm^3, 122 mmol) was added and the stirred mixture was cooled to ice bath temperature prior to the addition of methanesulphonyl chloride (5.2 cm^3, 67 mmol). The ice bath was removed and the mixture heated under reflux for 2h. A further 2 equivalents of triethylamine (17 cm^3, 122 mmol) were added and heating was continued until t.l.c. analysis indicated that the reaction had gone to completion. After cooling, the mixture was filtered to remove insoluble material and the solvents were removed *in vacuo*. The crude oil was chromatographed on silia gel with ethyl acetate-petrol (60-80°C) (1:3) as the eluant to afford the diene (50) (R_F 0.80, solv. 1) as an oil (6.35 g, 72%); δ_H (270 MHz; $CDCl_3$) 5.27 (1 H, d, J_{cis} 9.8 Hz, 4-H), 5.45 (1 H, d, J_{trans} 16.5 Hz, 4-H), 6.55 (2 H, m, 2-H, 3 H), 7.08 (1 H, dd, $J_{4',5'}$ 7.5, $J_{5',6'}$ 4.5 Hz, 5'-H), 7.25 (1 H, d, $J_{3',4'}$ 7.5 Hz, 3'-H), 7.25 (1 H, m, 1-H), 7.58 (1 H, td, $J_{3',4',5'}$ 7.5, $J_{4',6'}$ 1.5 Hz, 4'-H), 8.54 (1 H, d, $J_{5',6'}$ 4.5 Hz, 6'-H); *m/z* (isobutane CI) 132 ($M+1$, 100%).[16]

Preparation of the isoxazoline (49).- The diene (50) (2.3 g, 17.6 mmol) and ethyl chloro-oximidoacetate (79) (4 g, 26.4 mmol) were dissolved in dry diethyl ether (100 cm^3) under nitrogen. A solution of triethylamine (3.68 cm^3, 26.4 mmol) in dry diethyl ether (50 cm^3) was added dropwise over ½h to the vigorously stirred reaction mixture causing precipitation of triethylamine hydrochloride. After stirring for a

further 1h, water (30 cm^3) was added and the organic layer was separated. The aqueous phase was washed twice with diethyl ether and the combined organic fractions were dried ($MgSO_4$) and concentrated to an oil. This was chromatographed on silica gel with ethyl acetate–petrol (60–80°C) (1:4) as eluant to afford *ethyl 5-[2-(2-pyridyl)ethenyl]isoxazoline-3-carboxylate (49)* (R_F 0.30, solv. 1) as an oil, (2.83 g, 65%) $\nu_{max.}$ ($CHCl_3$) 2 900w (C–H), 1 720s (C=O), 1 590 (C=C), 1 380w, 1 350w, 1 125, 970, 920 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.36 (3 H, t, *J* 6.8 Hz, $CO_2CH_2CH_3$), 3.17 (1 H, dd, $J_{4,4(gem)}$ 17.1, $J_{4,5(vic)}$ 11.4 Hz, 4–H), 3.46 (1 H, dd, $J_{4,4(gem)}$ 17.1, $J_{4,5(vic)}$ 8.6 Hz, 4–H), 4.35 (2 H, q, *J* 6.8 Hz, $CO_2CH_2CH_3$), 5.46 (1 H, m, 5–H), 6.73 (1 H, d, $J_{1',2'}$ 16 Hz, 1'–H), 6.80 (1 H, d, $J_{1',2'}$ 16 Hz, 2'–H), 7.18 (1 H, ddd, $J_{4'',5''}$ 8, $J_{5'',6''}$ 5, $J_{3'',5''}$ 1.1 Hz, 5''–H), 7.29 (1 H, d, $J_{3'',4''}$ 8 Hz, 3''–H), 7.66 (1 H, td, $J_{3'',4'',5''}$ 8, $J_{4'',6''}$ 2.3 Hz, 4''–H), 8.56 (1 H, d, $J_{5'',6''}$ 5 Hz, 6''–H); δ_C (67.8 MHz; $CDCl_3$) 13.9 (q, $CO_2CH_2CH_3$), 39.1 (t, 4–C), 61.9 (t, $CO_2CH_2CH_3$), 83.3 (d, 5–C), 122.3 (d, 5''–C), 122.7 (d, 3''–C), 129.9 (d, 1'–C), 132.4 (d, 2'–C), 136.6 (d, 4''–C), 149.3 (d, 6''–C), 151.0 (s, 3–C), 153.7 (s, 2''–C), 160.2 (s, $CO_2CH_2CH_3$); *m/z* (low eV EI) 246 (M^+, 100%), 229 (50), 216 (42) (Found: M^+, 246.0995. $C_{13}H_{14}N_2O_3$ requires *M*, 246.1003).

Oxidation of the isoxazoline (49) to the isoxazole (45).– The isoxazoline (49) (1 g, 4 mmol) was dissolved in dry benzene (25 cm^3, distilled from CaH_2) and in this was slurried γ–active manganese dioxide (5 g). The mixture was heated under reflux with stirring for 2h, and the water formed was removed by the use of a Dean–Stark trap. At the end of this time t.l.c. analysis indicated a complete conversion to the product and the slurry was filtered through celite. This was washed with dichloromethane and the combined filtrates were concentrated to afford an oil. This was chromatographed on silica gel with ethyl acetate–petrol (60–80°C) (1:3) as eluant to yield the isoxazole (45) as a colourless crystalline solid (660 mg, 67%) (spectral data as previously recorded).

Preparation of the isoxazole (83).- The isoxazole (45) (139 mg, 0.57 mmol) was dissolved in methanol (30 cm^3) and to this solution was added 10% palladium on charcoal (50 mg). The slurry was stirred under hydrogen gas (1 atmosphere) at room temperature. After 1h, t.l.c. analysis showed the presence of a new compound with no remaining starting material. The reaction mixture was diluted with ethyl acetate (50 cm^3) and filtered through celite. The filtrate was concentrated *in vacuo* and the resultant oil was chromatographed on silica gel eluting with ethyl acetate–petrol (60–80°C) (1:1) to yield *ethyl 5-[2-(2-pyridyl)ethyl]isoxazole-3-carboxylate (83)* (R_F 0.45, solv. 1) as a clear oil (119 mg, 85%); $\lambda_{max.}$ (EtOH) 203 (ϵ 8 810 $dm^3\ mol^{-1}\ cm^{-1}$), 248 (6 300), 253 (6 420), 259 (6 030), 265sh nm (3 800); $\nu_{max.}$ ($CHCl_3$) 2 920 (C-H), 1 720s (C=O), 1 585 (C=C), 1 430br, 1 090, 990 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.41 (3 H, t, *J* 4.6 Hz, $CO_2CH_2CH_3$), 3.20 (2 H, t, $J_{1',2'}$ 5 Hz, 1'-H), 3.32 (2 H, t, $J_{1',2'}$ 5 Hz, 2'-H), 4.42 (2 H, q, *J* 4.6 Hz, $CO_2CH_2CH_3$), 6.40 (1 H, s, 4-H), 7.13 (1 H, d, $J_{3'',4''}$ 5 Hz, 3''-H), 7.16 (1 H, dd, $J_{4'',5''}$ 5, $J_{5'',6''}$ 3, 5''-H), 7.60 (1 H, td, $J_{3'',4'',5''}$ 5, $J_{4'',6''}$ 1.2 Hz, 4''-H), 8.56 (1 H, dm, $J_{5'',6''}$ 3 Hz, 6''-H); δ_C (67.8 MHz; $CDCl_3$) 14.0 (q, $CO_2CH_2CH_3$), 26.0 (t, 1'-C), 35.2 (t, 2'-C), 61.9 (t, $CO_2CH_2CH_3$), 101.7 (d, 4-C), 121.6 (d, 5''-C), 122.8 (d, 3''-C), 136.5 (d, 4''-C), 149.3 (d, 6''-C), 156.2 (s, 5-C), 158.8 (s, 3-C), 160.0 (s, 2''-C), 174.4 (s, $CO_2CH_2CH_3$); *m/z* (low eV EI) 246 (M^+, 35%), 173 (13, $M - CO_2Et$), 147 (100) (Found: M^+, 246.0992. $C_{13}H_{14}N_2O_3$ requires *M*, 246.1003).

Preparation of the isoxazoline (85).- The isoxazoline (49) (200 mg) was dissolved in ethanol (20 cm^3) and to this solution was added 10% palladium on charcoal (20 mg). The slurry was stirred under hydrogen gas (1 atmosphere) at room temperature. After 2h, t.l.c. analysis indicated complete conversion of starting material to a compound of slightly lower R_F. The mixture was diluted with ethyl acetate (50 cm^3) and filtered through celite. The solvents were removed *in vacuo* to afford an oil

which was chromatographed on silica gel with ethyl acetate–petrol (60–80°C) (1:1) as the eluant to yield *ethyl 5-[2-(2-pyridyl)ethyl]isoxazoline-3-carboxylate (85)* (R_F 0.20, solv. 1) as a clear oil (172 mg, 86%); (Found: C, 62.6; H, 6.65; N, 11.4. $C_{13}H_{16}N_2O_3$ requires C, 62.9; H, 6.45; N, 11.3%); $\nu_{max.}$ ($CHCl_3$) 2 930s (C–H), 1 710vs (C=O), 1 590s (C=C), 1 430, 1 380, 1 335, 1 125s, 1 000, 935s, 910 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.36 (3 H, t, *J* 7.5 Hz, $CO_2CH_2CH_3$), 2.15 (2 H, m, 1'–H), 2.90 (2 H, m, 2'–H), 2.91 (1 H, dd, $J_{4,4(gem)}$ 18, $J_{4,5(vic)}$ 7.5 Hz, 4–H), 3.28 (1 H, dd, $J_{4,4(gem)}$ 18, $J_{4,5(vic)}$ 11.2 Hz, 4–H), 4.34 (2 H, q, *J* 7.5 Hz, $CO_2CH_2CH_3$), 4.85 (1 H, m, 5–H), 7.16 (1 H, ddd, $J_{4",5"}$ 7.5, $J_{5",6"}$ 5.2, $J_{3",5"}$ 1.5 Hz, 5"–H), 7.20 (1 H, d, $J_{3",4"}$ 7.5 Hz, 3"–H), 7.62 (1 H, td, $J_{3",4",5"}$ 7.5, $J_{4",6"}$ 2.3 Hz, 4"–H), 8.53 (1 H, dm, $J_{5",6"}$ 5.2 Hz, 6"–H); δ_C (67.8 MHz; $CDCl_3$) 13.9 (q, $CO_2CH_2CH_3$), 33.4 (t, 1'–C), 34.6 (t, 2'–C), 38.3 (t, 4–C), 61.8 (t, $CO_2CH_2CH_3$), 83.1 (d, 5–C), 121.3 (d, 5"–C), 122.9 (d, 3"–C), 136.5 (d, 4"–C), 149.1 (d, 6"–C), 151.3 (s, 3–C), 160.2 (s, 2"–C), 160.6 (s, $CO_2CH_2CH_3$); *m/z* (isobutane CI) 249 (*M+1*, 82%), 175 (25), 106 (54), 93 (100).

Preparation of the hydrazide (87).– The isoxazole ester (45) (125 mg, 0.51 mmol) and hydrazine hydrate (0.025 cm^3, 0.51 mmol) were dissolved in ethanol (3 cm^3). The mixture was heated under reflux for 2h after which time t.l.c. analysis indicated starting material remaining. A further 2 eq of hydrazine hydrate (0.05 cm^3, 1.02 mmol) were added, the mixture heated for another 2h and allowed to cool. The solid which crystallised from the reaction mixture was collected and dried to yield the crude product (80 mg). This was preadsorbed on to silica gel and chromatographed with ethyl acetate as the eluant. *5-[2-(2-Pyridyl)ethenyl]isoxazole-3-hydrazinecarboxylate (87)* (R_F 0.30, EtOAc) was isolated as a colourless powder (40 mg, 35%), m.p. 145–155°C (decomp.) $\nu_{max.}$ (nujol) 3 315 and 3 240 (N–H), 1 670s (amide 1), 1 630, 1 595, 1 570, 1 525, 1 260, 990, 940 cm^{-1}; δ_H [270 MHz, $(CD_3)_2SO$] 4.69 (2 H, br s, NH_2), 7.07 and 7.15 (1 H, 2 s (4:1), 4–H), 7.38 (1 H, ddd, $J_{4",5"}$ 7.5,

$J_{5'',6''}$ 5.25, $J_{3'',5''}$ 1.5 Hz, 5''-H), 7.54 and 7.57 [1 H, 2 d (4:1), $J_{1',2'}$ 16.5 Hz, 1'-H), 7.67 (1 H, d, $J_{1',2'}$ 16.5 Hz, 2'-H), 7.67 (1 H, d, $J_{3'',4''}$ 7.5 Hz, 3''-H), 7.87 (1 H, td, $J_{3'',4'',5''}$ 7.5, $J_{4'',6''}$ 2.3 Hz, 4''-H), 8.65 (1 H, dm, $J_{5'',6''}$ 5.25 Hz, 6''-H), 10.11 and 10.82 [1 H, 2 s, (4:1), CO_2NH NH_2]; δ_C [270 MHz; $(CD_3)_2SO$] 102.6 (d, 4-C), 115.9 (d, 1'-C), 124.0 (d, 5''-C), 124.1 (d, 3''-C), 134.5 (d, 2'-C), 137.3 (d, 4''-C), 150.0 (d, 6''-C), 153.0 (s, 2''-C), 157.8 (s, 5-C), 162.7 (s, 3-C), 168.8 (s, *C* ONHNH$_2$); *m/z* (70 eV EI) 230 (M^+, 100%), 199 (18, M – NHNH$_2$), 171 (15), 132 (30), 117 (16), 104 (20), 78 (25) (Found: M^+, 230.2466. $C_{11}H_{10}N_4O_2$ requires M, 230.2256).

Preparation of the acyl azide (88).- The hydrazide (87) (500 mg, 2.2 mmol) was dissolved in 2M HCl (20 cm^3) with stirring at -5°C. Diethyl ether (20 cm^3) was added initially, and a solution of sodium nitrite (152 mg, 2.2 mmol) in water (5 cm^3) was dripped into the vigorously stirred mixture, keeping the temperature below 5°C during the addition. The mixture was stirred for 5 minutes, after which time t.l.c. analysis indicated complete conversion to the new compound. Sodium carbonate was added until the solution was just basic and the diethyl ether layer was separated. The aqueous phase was extracted several times with diethyl ether, the combined organic phases were washed with brine, dried ($MgSO_4$), and the solvents removed to yield *5-[2-(2-pyridyl)ethenyl]isoxazole-3-azidocarboxylate (88)* (R_F 0.45, solv. 2) as a solid (398 mg, 75%), $\nu_{max.}$ ($CHCl_3$) 2 160s (N_3), 1 700s (C=O), 1 585 (C=C), 1 440, 1 165, 960, 850 cm^{-1}; δ_H (60 MHz; $CDCl_3$) 6.80 (1 H, s, 4-H), 7.20-8.00 (5 H, m, 1'-H and 2'-H, 3''-, 4''-, and 5''-H), 8.75 (1 H, dm, $J_{5'',6''}$ 5 Hz, 6''-H); *m/z* (low eV EI) 241 (M^+, 100%), 213 (51, M- N_2), 158 (38), 145 (21), 117 (36).

Preparation of the 3-isoxazolamine carbamate (89).- The acyl azide (88) (338 mg, 1.4 mmol) was dissolved in *t*-butanol (20 cm^3) and this was heated under reflux for 1h. After this time t.l.c. analysis indicated complete conversion to the product, and after cooling the reaction mixture the solvents were removed *in vacuo*. The

resulting solid was chromatographed on silica gel with ethyl acetate–petrol (60-80°C) (1:3) as eluant to yield *t-butyl 5-[2-(2-pyridyl)ethenyl]-3-isoxazolamine carbamate (89)* (R_F 0.65, solv. 1) as a colourless crystalline solid (228 mg, 57%), m.p. 180–182°C (Found:C, 62.5; H, 5.9; N, 14.8. $C_{15}H_{17}N_3O_3$ requires C, 62.7; H, 5.95; N, 14.6%); $\lambda_{max.}$ (EtOH) 204 (ϵ 43 050 dm^3 mol^{-1} cm^{-1}), 241 (15 830), 264sh (19 610), 269 (20 230), 311 (25 930), 325sh nm (11 960); $\nu_{max.}$ ($CHCl_3$) 3 400 (N–H), 1 730s (C=O), 1 590s (C=C), 1 460w, 1 410w, 1 150s, 960w cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.54 [9 H, s, $CO_2C(CH_3)_3$], 6.86 (1 H, br s, 4-H), 7.22–7.24 (1 H, br s, N*H*), 7.23 (2 H, ddd, $J_{4'',5''}$ 8, $J_{5'',6''}$ 4.5, $J_{3'',5''}$ 1.1 Hz, 5''–H), 7.33 (1 H, d, $J_{1',2'}$ 16 Hz, 1'–H), 7.35 (1 H, d, $J_{3'',4''}$ 8 Hz, 3''–H), 7.50 (1 H, d, $J_{1',2'}$ 16 Hz, 2'–H), 7.70 (1 H, td, $J_{3'',4'',5''}$ 8, $J_{4'',6''}$ 2 Hz, 4''–H), 8.64 (1 H, dm, $J_{5'',6''}$ 4.5 Hz, 6''–H); δ_C (67.8 MHz; $CDCl_3$) 28.2 [q, $CO_2C(CH_3)_3$], 81.9 [s, $CO_2C(CH_3)_3$], 96.5 (d, 4–C), 116.9 (d, 1'–C), 123.3 (d, 5''–C), 123.7 (d, 3''–C), 133.4 (d, 2'–C), 136.8 (d, 4''–C), 149.9 (d, 6''–C), 151.8 (s, 5–C), 153.5 (s, 2''–C), 158.8 (s, 3–C), 167.9 [s, $CO_2C(CH_3)_3$]; *m/z* (low eV EI) 287 (M^+, 100%), 231 [45, $M-C{=}C(CH_3)_2$], 187 [58, $M-CO_2C(CH_3)_3$].

7.4 Experimental to Chapter 4.

Attempted photocyclisation of the isoxazole (45). The isoxazole (45) (100 mg) was dissolved in dry benzene (1 000 cm^3, distilled from CaH_2) and to this solution was added a catalytic amount of iodine. The mixture was put into a water cooled photochemical reactor (of capacity 1 000 cm^3) and after purging with nitrogen gas for 1h was irradiated with a 400 W medium pressure lamp within a quartz tube for 8h. After this time the solvents were removed *in vacuo* to afford a yellow oil and this was chromatographed on silica gel with ethyl acetate–petrol (60–80°C) (1:9) as eluant. However, no compound with interpretable spectral data was isolated from the mixture.

The reaction was repeated under identical conditions except that a pyrex inner sleeve was used to hold the lamp. Once again however, nothing was isolated from the reaction mixture which we were able to identify and the experiment was therefore abandoned.

Attempted photocyclisation of the isoxazole[17] *(45).*- The isoxazole (45) (50 mg, 0.2 mmol), *p*-nitrobenzoic acid (33 mg, 0.2 mmol), and triethylamine (0.03 cm^3, 0.22 mmol) were dissolved in dry acetonitrile (200 cm^3) and to this was added 10% palladium on charcoal (5 mg). The mixture was stirred in a water cooled photochemical reactor (of capacity 200 cm^3) purged with nitrogen gas for ½h, prior to irradiation with a 125W medium pressure lamp for 18h. After this time the reaction mixture was concentrated to an oil and chromatographed on silica gel with ethyl acetate-petrol (60-80°C) as eluant. This resulted in the isolation of unidentified decomposition products only.

The reaction was repeated using identical conditions except that it was monitored by t.l.c. analysis at 2h intervals. After 8h the starting isoxazole had almost completely disappeared and the reaction was worked up as before. Nothing identifiable was obtained after column chromatography; the experiment was therefore abandoned.

Attempted photocyclisation of the isoxazole (89). The isoxazole (50 mg) was dissolved in dry benzene-methanol (3:1) (400 cm^3) and to this solution was added a catalytic amount of iodine. The mixture was put into a photochemical reactor (of capacity 400 cm^3) and after purging with nitrogen gas for 1h was irradiated with a 400 W medium pressure lamp within a pyrex tube for 8h. After this time the solvents were removed *in vacuo* to afford an oil and this was chromatographed on silica gel with methanol-chloroform (1:9) as eluant. However, only unidentified decomposition

products were isolated; the experiment was therefore abandoned.

Preparation of (E)-4-(2-pyridyl)-3-buten-2-one[18] *(105).*- A hydrogenation autoclave of 300 cm^3 capacity was charged with 2-pyridinecarboxaldehyde (7.13 cm^3, 75 mmol), 1-triphenylphosphoranylidene-2-propanone (23.88 g, 75 mmol) and xylene (175 cm^3). The autoclave was sealed and filled with hydrogen gas to a pressure of 7 atmospheres and the mixture was agitated and maintained at 150°C for 18h. After allowing to cool and venting, the mixture was transferred to a round bottomed flask and the solvents were removed in vacuo. Ether (100 cm^3) was added and the mixture cooled to 4°C for 18h. The triphenylphosphonium oxide precipitate was removed by filtration and the filtrate concentrated to an oil. This was chromatographed on silica gel with ethyl acetate in petrol (60-80°C) (1:3) as the eluant to afford the product (105) as an oil (8.95g, 81%); δ_H (270 MHz; $CDCl_3$) 2.40 (3 H, s, 1-H), 7.17 (1 H, d, $J_{1',2'}$ 16 Hz, 1'-H), 7.28 (1 H, m, 5'-H), 7.50 (1 H, d, $J_{3',4',5'}$ 7 Hz, 3'-H), 7.54 (1 H, d, $J_{1',2'}$ 16 Hz, 2'-H), 7.75 (1 H, td, $J_{3',4',5'}$ 7, $J_{4',6'}$ 1.5 Hz, 4'-H), 8.67 (1 H, dm, $J_{5',6'}$ 4 Hz, 6'-H); *m/z* (low eV EI) 147 (M^+, 100%).

Attempted preparation of the ethenylthiazolamine (41)-1.- Formamidine disulphide dihydrochloride (55) (200 mg, 0.7 mmol) sodium bicarbonate (60 mg, 0.7 mmol) and the enone (105) (200 mg, 1.4 mmol) were heated in the absence of solvent at 100°C for 1h. This resulted in an intractible black tar which contained only decomposition products. The experiment was therefore abandoned.

Attempted preparation of the ethenylthiazolamine (41)-2.- The enone (105) (100 mg, 0.7 mmol) and thiourea (106 mg, 1.4 mmol) were dissolved in dioxane (5 cm^3) and the mixture was heated almost to reflux with stirring. Iodine (178 mg, 0.7 mmol) was added and heating was continued for a further 2h. This however resulted

in an inseperable mixture and was therefore abandoned.

Attempted preparation of the bromomethylenone (106).- The enone (105) (197 mg, 1.3 mmol) was stirred in acetic acid (3 cm^3) at 50°C under nitrogen. Bromine (0.07 cm^3, 1.3 mmol) in acetic acid (2 cm^3) was added slowly dropwise, keeping the reaction temperature at 70°C. The mixture was heated at 70°C for 2h after which time t.l.c. analysis indicated the disappearance of starting material. After cooling, ethyl acetate (20 cm^3) and sodium bisulphite (500 mg) were added, and basification was accomplished with saturated sodium carbonate solution (20 cm^3). The aqueous layer was extracted several times with ethyl acetate, the organic phase was washed with brine, dried ($MgSO_4$) and concentrated to an oil. This was chromatographed on silica gel with ethyl acetate–petrol (60–80°C) (1:3) as eluant to yield a compound (76 mg, 26%; R_F 0.32, solv. 2) assigned as *4-bromo-4-(2-pyridyl)-3-buten-2-one (109)*; δ_H (270 MHz; $CDCl_3$) 2.10 (3 H, s, CH_3), 6.88 (1 H, s, 3–H), 7.28 (1 H, ddd, $J_{4',5'}$ 7.2, $J_{5',6'}$ 4.5, $J_{3',5'}$ 1 Hz, 5'–H), 7.56 (1 H, d, $J_{3',4'}$ 7.2 Hz, 3'–H), 7.76 (1 H, td, $J_{3',4'5'}$ 7.2, $J_{4',6'}$ 1.8 Hz, 4'–H), 8.55 (1 H, dm, $J_{5',6'}$ 4.5 Hz, 6'–H); *m/z* (isobutane CI) 228 [*M+1* (^{81}Br), 98%], 226 [*M+1* (^{79}Br), 100], 212 (34), 210 (34), 148 (25), 104 (25).

Preparation of chloroacetonyltriphenylphosphoniumchloride[19] *(112).*- 1,3-Dichloroacetone (111) (96.5 g, 760 mmol) and triphenylphosphine (200 g, 760 mmol) were dissolved in THF (400 cm^3) and the solution was heated under reflux with stirring for 4h. At the end of this time the mixture was allowed to cool and the product (112) collected by filtration, washed with diethyl ether and dried (244.3 g, 83%), m.p. 205–208°C (lit.[19] 210–212) (Found: C, 64.3; H, 4.95. Calc. for $C_{21}H_{19}Cl_2OP$: C, 64.45; H, 4.9%).

Preparation of 3-chloro-1-triphenylphosphoranylidene-2-propanone[19] *(110).*-

A solution of sodium carbonate (32.7 g, 308 mmol) in water (200 cm^3) was added fairly rapidly to a vigorously stirred solution of the triphenylphosphoniumchloride (112) (240 g, 617 mmol) in methanol (300 cm^3). After a few seconds effervescence occured and the product precipitated as a white solid. This was stirred for 5 minutes before water (1000 cm^3) was added and the mixture allowed to stand for ½h. The ylid (110) was collected and dried as a colourless solid (215 g, 98%), m.p. 175–178°C (lit. 179–180°C) (Found: C, 71.1; H, 5.25. Calc. for $C_{21}H_{18}ClOP$: C, 71.5; H, 5.15%).

Preparation of the chloromethylenone (113).- The ylid (110) (53.6 g, 152 mmol) and 2-pyridinecarboxaldehyde (14.4 cm^3, 151 mmol) were dissolved in dichloromethane (300 cm^3) and stirred at room temperature for 24h. Analysis by t.l.c. showed that the reaction had gone to completion and the solvents were removed *in vacuo*. Ethyl acetate was added to the amorphous mixture and this was heated to effect solution of the products. The solution was filtered and allowed to cool, resulting in crystallisation of triphenylphosphine oxide. This was collected and the filtrate concentrated and chromatographed on silica gel with ethyl acetate-petrol (60-80°C) (1:4) as eluant to yield *(E)-1-chloro-4-(2-pyridyl)-3-buten-2-one (113)* (R_F 0.55, solv. 1) as a solid (18.5 g, 67%), m.p. 48–49°C; $\nu_{max.}$ ($CHCl_3$) 2 945 (C-H), 1 675s (enone C=O), 1 615s, 1 590s (C=C), 1 465w, 1 425w, 1 400w, 1 315s, 1 165, 1 150, 1 070s, 980s cm^{-1}; δ_H (270 MHz; $CDCl_3$) 4.35 (2 H, s, C*H*$_2$Cl), 7.32 (1 H, ddd, $J_{4',5'}$ 7.5, $J_{5',6'}$ 4.5, $J_{3',5'}$ 1 Hz, 5'-H), 7.43 (1 H, d, $J_{3,4}$ 16 Hz, 3-H), 7.48 (1 H, d, $J_{3',4'}$ 7.5 Hz, 3'-H), 7.70 (1 H, d, $J_{3,4}$ 16 Hz, 4-H), 7.76 (1 H, td, $J_{3',4',5'}$ 7.5, $J_{4',6'}$ 2 Hz, 4'-H), 8.68 (1 H, dm, $J_{5',6'}$ 4.5 Hz, 6'-H); δ_C (67.8 MHz; $CDCl_3$) 47.7 (t, *C*H_2Cl), 124.7 (d, 5'-C), 125.1 (d, 3'-C), 125.2 (d, 3-C), 136.8 (d, 4'-C), 143.2 (d, 4-C), 150.2 (d, 6'-C), 152.3 (s, 2'-C), 191.2 (s, *C*=O); *m/z* (isobutane CI) 184 [*M+1* (^{37}Cl), 35%], 182 [*M+1* (^{35}Cl), 100], 148 (30), 132 (80) [Found: M^+ (^{37}Cl), 183.0226. $C_9H_8{}^{37}ClNO$ requires *M*, 183.0264. Found: M^+ (^{35}Cl), 181.0250. $C_9H_8{}^{35}ClNO$ requires *M*, 181.0293].

Preparation of the ethenylthiazolamine hydrochloride (114).- The chloromethylenone (113) (18.33 g, 101 mmol) and thiourea (7.7 g, 101 mmol) were dissolved in *p*-dioxane (40 cm^3) and ethanol (60 cm^3). The mixture was heated just to reflux temperature for 2h, until t.l.c. analysis indicated the presence of product and depletion of starting materials. The mixture was allowed to cool and filtered to yield *4-[2-(2-pyridyl)ethenyl]-2-thiazolamine hydrochloride (114)* (R_F 0.45, solv. 3) as a yellow solid. This was recrystallised from ethanol (24 g, 99%) m.p. 198–200°C; (Found: C, 47.3; H, 4.3; Cl, 15.35; N, 16.55; S, 12.5. $C_{10}H_{10.1}Cl_{1.1}N_3S.½H_2O$ requires C, 47.6; H, 4.4; Cl, 15.45; N, 16.65; S, 12.7%.) $\lambda_{max.}$ (EtOH) 205 (ϵ 19 470 $dm^3\ mol^{-1}\ cm^{-1}$), 257 (23 900), 328 nm (20 830); $\nu_{max.}$ (nujol) 3 260br (H_2O) 3 100 (N–H), 2 680br ($N^+ - H$), 1 600, 1 545, 1 355, 1 280, 1 165w, 1 125w, 980w, 960w, 765w, 720w cm^{-1}; δ_H [270 MHz; $(CD_3)_2SO$] 7.10 (1 H, s, 5–H), 7.33 (1 H, d, $J_{1',2'}$ 15.75 Hz, 1'–H), 7.62 (1 H, convergent dd, $J_{4'',5''}$ 8.25, $J_{5'',6''}$ 5.25 Hz, 5''–H), 7.70 (1 H, d, $J_{1',2'}$ 15.75 Hz, 2'–H), 7.80–8.60 (2 H, br s, N*H*$_2$), 8.02 (1 H, d, $J_{3'',4''}$ 8.25 Hz, 3''–H), 8.23 (1 H, td, $J_{3'',4'',5''}$ 8.25, $J_{4'',6''}$ 1.5 Hz, 4''–H), 8.66 (1 H, dm, $J_{5'',6''}$ 5.25 Hz, 6''–H).

Preparation of the ethenylthiazolamine (41).- The ethenylthiazolamine hydrochloride (114) (7.5 g, 31 mmol) was stirred in 10% solution of ammonia in ethanol (25 cm^3) for 2h. The free amine was collected by filtration, washed with ethanol and chromatographed on silica gel with 1% triethylamine in ethyl acetate as eluant to yield *4-[2-(2-pyridyl)ethenyl]-2-thiazolamine* (41) (R_F 0.45, solv. 3) as a solid (6 g, 95%) m.p. 175–177°C; (Found: C, 59.2; H, 4.4; N, 20.7. $C_{10}H_9N_3S$ requires C, 59.1; H, 4.5; N, 20.7%.); $\lambda_{max.}$ (EtOH) 206 (ϵ 8 830 $dm^3\ mol^{-1}\ cm^{-1}$), 257 (17 440), 329 nm (16 180); $\nu_{max.}$ (nujol) 3 250 and 3 100 (N–H), 1 650, 1 620, 1 580, 1 540, 1 430, 1 350, 1 290w, 1 270w, 1 205w, 1 150w, 1 125w 1 090w, 1 050w, 995w, 960, 855, 765 cm^{-1}; δ_H [270 MHz; $(CD_3)_2SO$] 6.77 (1 H, s, 5'–H), 7.10 (1 H, d, $J_{1',2'}$ 16 Hz, 1'–H), 7.11 (2 H, br s, N*H*$_2$), 7.21 (1 H, ddd, $J_{4'',5''}$ 7.9, $J_{5'',6''}$ 4.5, $J_{3'',5''}$ 1.1 Hz, 5''–H), 7.37 (1

H, d, $J_{1',2'}$ 16 Hz, 2'-H), 7.47 (1 H, d, $J_{3'',4''}$ 7.9 Hz, 3''-H), 7.74 (1 H, td, $J_{3'',4'',5''}$ 7.9, $J_{4'',6''}$ 1.9 Hz, 4''-H), 8.53 (1 H, dm, $J_{5'',6''}$ 4.5 Hz, 6''-H); δ_C [67.8 MHz; $(CD_3)_2SO$] 108.8 (d, 5-C), 122.3 (d, 5''-C), 122.4 (d, 3''-C), 126.1 (d, 1'-C), 128.2 (d, 2'-C), 136.9 (d, 4''-C), 149.4 (d, 6''-C), 149.6 (s, 4-C), 155.4 (s, 2''-C), 168.3 (s, 2-C); *m/z* (low eV EI) 203 (M^+, 100%), 202 (45).

Attempted photocyclisation of the ethenylthiazolamine[17] *(41).*- The ethenylthiazolamine (41) (100 mg, 0.5 mmol), *p*-nitrobenzoic acid (84 mg, 0.5 mmol), and triethylamine (0.07 cm^3, 0.55 mmol) were dissolved in dry acetonitrile (200 cm^3) and to this was added 10% palladium on charcoal (50 mg). The mixture was stirred in a water cooled photochemical reactor (of capacity 200 cm^3) and purged with nitrogen gas for 2h. This was irradiated with a 125W medium pressure lamp in a pyrex sleeve for 18h. After this time the reaction mixture was concentrated to an oil and chromatographed on silica gel with 1% triethylamine in ethyl acetate as eluant. This resulted in the isolation of unidentiafiable decomposition products only; the experiment was therefore abandoned.

Attempted photocyclisation of the ethenylthiazolamine hydrochloride[20] *(114).*- The ethenylthiazolamine hydrochloride (114) (110 mg, 0.5 mmol) was dissolved in ethanol (350 cm^3) and the solution was purged with nitrogen gas for 1h in a water cooled photochemical reactor of 400 cm^3 capacity. The solution was irradiated with a 400W medium pressure mercury lamp for 3½h. Analysis by t.l.c. indicated that there was no longer starting material present, and the solvents were removed *in vacuo*. The residue was chromatographed on silica gel with 1% triethylamine in ethyl acetate as eluant. This yielded only decomposition products, however, and the experiment was therefore abandoned.

Attempted photocyclisation of the ethenylthiazolamine[20] *(41).*- The ethenylthiazolamine (41) (100 mg, 0.5 mmol) was dissolved in ethanol (350 cm^3) and the solution was purged with nitrogen gas for 1h in a water cooled photochemical reactor of 400 cm^3 capacity. The solution was irradiated with a 400W medium pressure mercury lamp for 3½h. Analysis by t.l.c. indicated that there was no longer starting material present and the solvents were removed *in vacuo.* The residue was chromatographed on silica gel with 1% triethylamine in ethyl acetate as eluant. As with the irradiation of the 2-thiazolamine hydrochloride, however, nothing which could be positively identified as an organic molecule was isolated and therefore the experiment was abandoned.

7.5 Experimental to Chapter 5.

Preparation of the N*-methylpyridinium iodide (119).*- The ethenylthiazolamine (41) (5.5 g, 27 mmol) was slurried in acetonitrile (100 cm^3) and heated to reflux temperature to effect solution. Iodomethane was added in five portions (approximately 2 cm^3 each) during the period of reflux (*ca.* 10h). After this time the yellow solid which had precipitated out was collected and dried (7.87 g). Analysis by t.l.c. indicated that this contained unreacted starting material as well as product, and this was therefore chromatographed on alumina with 2-propanol–ethyl acetate (1:3) as eluant to yield *(E)-4-{2-[2-(N-methyl)pyridinium]ethenyl}-2-thiazolamine iodide* (119) (R_F 0.35, solv. 4) as a yellow crystalline solid (6.5 g, 69%), m.p. 233–235°C (from methanol) (Found: C, 37.9; H, 3.45; N, 12.1. $C_{11}H_{12}IN_3S$ requires C, 38.3; H, 3.5; N, 12.2%.); $\lambda_{max.}$ (EtOH) 207 (ϵ 22 610 dm^3 mol^{-1} cm^{-1}), 268 (8 660), 285sh (6 900), 390 nm (6 560); $\nu_{max.}$ (nujol) 3 277 and 3 137 (N–H), 1 610 (C=C), 1 570, 1 525, 1 360, 1 310w, 1 270, 1 180, 1 140w, 980, 860, 765, 720 cm^{-1}; δ_H [270 MHz; $(CD_3)_2SO$] 4.28 (3 H, s, CH_3), 7.19 (1 H, s, 5–H), 7.25 (1 H, d, $J_{1',2'}$ 15.5 Hz, 1'–H),

7.30–7.50 (2 H, br s, NH_2), 7.71 (1 H, d, $J_{1',2'}$ 15.5 Hz, 2'–H), 7.86 (1 H, m, 5''–H), 8.45 (2 H, m, 3''–H, 4''–H), 8.93 (1 H, d, $J_{5'',6''}$ 6 Hz, 6''–H); δ_C [67.8 MHz; $(CD_3)_2SO$] 45.7 (q, CH_3), 115.6 (d, 5–C), 116.7 (d, 1'–C), 124.5 (d, 5''–C), 124.6 (d, 3''–C), 135.5 (d, 2'–C), 144.1 (d, 6''–C), 145.9 (d, 4''–C), 148.1 (s, 2''–C), 152.5 (s, 4–C), 168.6 (s, 2–C).

Sodium borohydride reduction of the N-*methylpyridinium iodide (119).*– The *N*–methylpyridinium iodide (119) (7.2 g, containing some unreacted starting material) was slurried in ethanol (100 cm^3) and to the stirred, cooled (0°C) solution was added sodium borohydride (1.58 g, 42 mmol) in portions. This resulted in effervescence and after a few minutes a homogeneous solution. The cooling bath was removed and the reddish solution stirred at room temperature for ½h. Acetone (10 cm^3) was added to quench any unreacted borohydride and the solvents were removed *in vacuo*. Ethyl acetate (30 cm^3) and 2M aqueous HCl (20 cm^3) were added to the amorphous solid and the aqueous phase was made slightly basic with sodium carbonate. The organic layer was separated and the aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated to afford an oil. This was chromatographed on silica gel with 1% triethylamine in dichloromethane as eluant to yield the ethenylthiazolamine (41) (669 mg). The solvent polarity was increased to 1% triethylamine in methanol–dichloromethane (1:19) to yield *4-[2-(N-methyl-1,2,3,6-tetrahydropyrid-2-yl)ethenyl]-2-thiazolamine* (120) (R_F 0.32, solv. 5) as a solid [2.3 g, 55% based on 6.53 g of the *N*–methylpyridinium iodide (119) used], m.p. 172°C (from ethanol) (Found: C, 57.35; H, 7.0; N, 18.3. $C_{11}H_{15}N_3S.½H_2O$ requires C, 57.4; H, 6.95; N, 18.3%.) $\lambda_{max.}$ (EtOH) 195 (ϵ 11 960 $dm^3\ mol^{-1}\ cm^{-1}$), 220 (28 110), 268 nm (14 490); $\nu_{max.}$ (KBr) 3 307vs and 3 123vs (N–H, H_2O), 2 798 (C–H), 1 649vs (C=C), 1 544vs (C=C), 1 505, 1 454, 1 392, 1 351vs, 1 236, 1 126s, 1 102, 1 044, 1 007, 969s, 850, 814,

686, 656 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 2.25 (2 H, m, 3''-H), 2.32 (3 H, s, C*H*$_3$), 2.94 (1 H, dm, $J_{6'',6''(gem)}$ 17 Hz, 6''-H), 3.02 (1 H, ddm, $J_{2'',3''(vic)}$ 14, $J_{2'',3''(vic)}$ 6.5 Hz, 2''-H), 3.25 (1 H, dm, $J_{6'',6''(gem)}$ 17 Hz, 6''-H), 5.38 or 5.95 (2 H, br s, N*H*$_2$), 5.69 (1 H, dm, $J_{4'',5''(cis)}$ 12 Hz, 5''-H), 5.77 (1 H, dm, $J_{4'',5''(cis)}$ 12 Hz, 4''-H), 6.25 (1 H, d, $J_{1',2'}$ 16 Hz, 2'-H), 6.31 (1 H, s, 5-H), 6.34 (1 H, d, $J_{1',2'}$ 16 Hz, 1'-H); δ_C (67.8 MHz; $CDCl_3$) 32.3 (t, 3''-C), 42.9 (q, *C*H$_3$), 53.0 (t, 6''-C), 62.0 (d, 2''-C), 104.9 (d, 5-C), 123.7 (d, 1'-C), 124.5 (d, 4''-C), 125.0 (d, 5''-C), 131.1 (d, 2'-C), 149.0 (s, 4-C), 167.8 (s, 2-C); *m/z* (low eV EI) 221 (M^+, 83%), 220 (31), 94 (100).

A lower running compound isolated as a water soluble oil (R_F 0.45, solv. 5) proved to be *4-[2-(N-methyl-1,2,3,6- tetrahydropyrid-2-yl)ethyl]-2-thiazolamine* (123) (96 mg, 2.3%); $\nu_{max.}$ (CH_2Cl_2) 3 481 and 3 386 (N-H), 3 032 (aromatic, vinylic C-H), 2 949s (aliphatic C-H), 2 781, 1 604vs (C=C), 1 517vs, 1 473w, 1 338, 1 270br, 1 157w, 1 050, 801, 660 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.65 (1 H, m, 2'-H), 1.95 (1 H, m, 3''-H), 2.02 (1 H, m, 2'-H), 2.20 (1 H, dm, $J_{3'',3''(gem)}$ 17 Hz, 3''-H), 2.35 (3 H, s, C*H*$_3$), 2.55 (3 H, m, 1'-H and 2''-H), 3.00 (1 H, dm, $J_{6'',6''(gem)}$ 17 Hz, 6''-H), 3.16 (1 H, dm, $J_{6'',6''(gem)}$ 17 Hz, 6''-H), 5.25 (2 H, br s, N*H*$_2$), 5.63 (1 H, dm, $J_{4'',5''(cis)}$ 11 Hz, 5''-H), 5.73 (1 H, dm, $J_{4'',5''(cis)}$ 11 Hz, 4''-H), 6.10 (1 H, s, 5-H); δ_C (67.8 MHz; $CDCl_3$) 28.1 (t, 2'-C), 28.8 (t, 3''-C), 29.6 (t, 1'-C), 40.5 (q, *C*H$_3$), 53.1 (t, 6''-C), 57.5 (d, 2''-C), 101.7 (d, 5-C), 124.5 (d, 4''-C), 124.6 (d, 5''-C), 152.7 (s, 4-C), 168.1 (s, 2-C); *m/z* (low eV EI) 223 (M^+, 15%), 97 (76), 96 (100) (Found: M^+, 223.1122. $C_{11}H_{17}N_3S$ requires *M*, 223.1142).

An altered work-up procedure resulted in improved yields of the ethenyl-tetrahydropyridine (120) (64%) and the ethyltetrahydropyridine (123) (14%). After the initial removal of solvents, the solid was acidified with the minimum of 2M HCl, basified (Na_2CO_3), 2-propanol added and the solvents again removed *in vacuo*. Methanol was added and this was filtered to remove inorganic solids before being concentrated to an oil and chromatographed as before.

Preparation of the amide (124).- The ethyltetrahydropyridine (123) (159 mg, 0.71 mmol) and acetic anhydride (0.1 cm^3, 1 mmol) were dissolved in dry acetonitrile (10 cm^3) and the solution was heated under reflux. After 1h, t.l.c. analysis indicated partial conversion of starting material to product and a further equivalent of acetic anhydride was added. Heating was continued for 1h and the mixture was allowed to cool. Triethylamine (1 cm^3) was added and the solution was stirred for 1h at room temperature. The solvents were removed *in vacuo* and the residue was chromatographed on silica gel with 1% ammonia in acetone–ethanol–chloroform (5:8:87) as eluant to yield *4-[2-(N-methyl-1,2,3,6-tetrahydropyrid-2-yl)ethyl]-2-thiazolacetamide* (124) as an oil (170 mg, 90%); $\nu_{max.}$ ($CHCl_3$) 3 407 (N-H), 3 000br (C-H), 1 680 (amide 1), 1 520br cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.70 (1 H, m, 2'-H), 2.05 (3 H, m, 3''-H, 2'-H, N*H*), 2.25 (4 H, m, 3''-H, NHCOC*H*$_3$), 2.40 (3 H, s, N-C*H*$_3$), 2.70 (3 H, m, 2''-H, 1'-H), 3.17 (1 H, dm, $J_{6'',6''(gem)}$ 18 Hz, 6''-H), 3.28 (1 H, dm, $J_{6'',6''(gem)}$ 18 Hz, 6''-H), 5.63 (1 H, dm, $J_{4'',5''(cis)}$ 10.5 Hz, 5''-H), 5.76 (1 H, dm, $J_{4'',5''(cis)}$ 10.5 Hz, 4''-H), 6.53 (1 H, s, 5-H); δ_C (67.8 MHz; $CDCl_3$) 22.8 (q, NHCO*C* H_3), 27.5 (t, 2'-C), 27.7 (t, 3''-C), 29.3 (t, 1'-C), 39.3 (q, N-*C*$_3$), 52.0 (t, 6''-C), 57.0 (d, 2''-C), 107.3 (d, 5-C), 123.4 (d, 4''-C), 124.1 (d, 5''-C), 150.3 (s, 4-C), 158.3 (s, 2-C), 168.3 (s, NH*C* OCH_3); *m/z* (isobutane CI) 266 (*M+1*, 100%), 97 (32), 96 (32) (Found: M^+, 265.1197. $C_{13}H_{19}N_3OS$ requires *M*, 265.1247).

Attempted preparation of the ethylthiazolamine (125) using heterogeneous catalysis.- The ethenylthiazolamine (41) (100 mg, 0.5 mmol) was dissolved in ethanol (20 cm^3) and in this was slurried 10% palladium on charcoal (10 mg). The mixture was stirred under hydrogen gas (1 atmosphere) at room temperature. Analysis by t.l.c. after several hours and again after several days showed the presence of starting material only, and the experiment was therefore abandoned. The procedure was repeated using raney nickel and platinum oxide (acetic acid solvent) as

the catalysts but in no case was a product seen.

Preparation of the ethylthiazolamine (125) using di-imide-1.- The ethenylthiazolamine (41) (100 mg, 0.5 mmol) and hydrazine hydrate (0.044 cm^3, 0.9 mmol) were dissolved in ethanol (5 cm^3). Into the solution was slurried selenium powder (4 mg, 0.05 mmol) and the mixture was stirred at room temperature in the presence of air for 24h. Dichloromethane (15 cm^3) was added, the mixture was filtered through celite to remove the selenium and the solvents were removed *in vacuo*. The residue was chromatographed on silica gel with ethyl acetate–petrol (60–80°C) (1:1) as the eluant to yield unreacted starting material (30 mg, 30%) followed by *4-[2-(2-pyridyl)ethyl]-2-thiazolamine (125)* (43 mg, 42% based on initial quantity of starting material) as a solid (R_F 0.30, solv.3). The experiment was repeated several times, a typical yield after column chromatography being 63% based on recovered starting material; m.p. 121°C [from EtOAc–petrol (60–80°C)] (Found: C, 58.7; H, 5.4; N, 20.55. $C_{10}H_{11}N_3S$ requires C, 58.5; H, 5.4; N, 20.5%); $\lambda_{max.}$ (EtOH) 203 (ϵ 21 810 dm^3 mol^{-1} cm^{-1}), 256 (11 400), 260 (11 5200), 266sh nm (8 815); $\nu_{max.}$ (KBr) 3 293 and 3 100 (N–H), 2 930 (C–H), 1 725w, 1 636, 1 594, 1 530s, 1 477, 1 443, 1 430, 1 336, 1 150, 1 115, 998, 979, 751s, 689 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 2.95 (2 H, m, 1'–H), 3.10 (2 H, m, 2'–H), 5.50 (2 H, br s, NH_2), 6.04 (1 H, s, 5–H), 7.10 (1 H, m, 5''–H), 7.13 (1 H, d, $J_{3'',4''}$ 7.9 Hz, 3''–H), 7.57 (1 H, td, $J_{3'',4'',5''}$ 7.9, $J_{4'',6''}$ 1.7 Hz, 4''–H), 8.54 (1 H, dm, $J_{5'',6''}$ 5 Hz, 6''–H); δ_C (67.8 MHz; $CDCl_3$) 31.5 (t, 1'–C), 37.3 (t, 2'–C), 102.5 (d, 5–C), 121.0 (d, 5''–C), 122.8 (d, 3''–C), 136.2 (d, 4''–C), 149.2 (d, 6''–C), 152.0 (s, 4–C), 161.1 (s, 2''–C), 167.7 (s, 2–C); *m/z* (low eV EI) 205 (M^+, 100%), 172 (7), 130 (38).

Attempted preparation of the ethylthiazolamine (125) using di-imide-2.- The ethenylthiazolamine (41) (100 mg, 0.5 mmol) and hydrazine hydrate (0.97 cm^3, 20

mmol) were dissolved in methanol (3 cm^3) containing two drops of saturated aqueous $CuSO_4$ solution and two drops of glacial acetic acid. A solution of sodium periodate (535 mg, 2.5 mmol) in water was added dropwise to the stirred solution over 1h. After the addition, t.l.c. analysis indicated the presence of starting material only, and so further equivalents of hydrazine and sodium periodate were added. The mixture was basified with sodium carbonate and extracted with ethyl acetate. The organic phase was dried ($MgSO_4$) and concentrated to an oil; however t.l.c. analysis once more revealed only starting material and the experiment was abandoned.

Preparation of the ethylthiazolamine (125) using di-imide-3.- The ethenylthiazolamine (41) (171 mg, 0.84 mmol) and *p*-toluenesulphonhydrazide (1.88 g, 10 mmol) in ethanol (8 cm^3) were heated with stirring under gentle reflux. Sodium acetate (1.64 g, 20 mmol) in water (8 cm^3) was added dropwise to the solution over a period of 5h (*ca.* 2 drops every ¼h). On completion of the addition t.l.c. analysis indicated the absence of starting alkene, and the reaction mixture was allowed to cool. Ammonium chloride (2 g) was added and the mixture was basified with sodium carbonate. This was extracted several times with dichloromethane, the combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated to afford an oil. This was chromatographed on silica gel with 1% triethylamine in ethyl acetate as eluant to yield the ethylthiazolamine (125) as a solid (33 mg, 19%).

Preparation of the ethylthiazolamine (125) using sodium hydrotelluride.- The ethenylthiazolamine (41) (27 g, 133 mmol) was dissolved in ethanol (350 cm^3) under nitrogen and in this solution was slurried tellurium powder (42.4 g, 332 mmol). The stirred mixture was cooled to 0°C and sodium borohydride (25.14 g, 665 mmol) was added carefully in small portions. A highly exothermic reaction occured which was controlled by use of an ice bath. Once the reaction had subsided the mixture was

heated gently under reflux for *ca.* 6h until t.l.c. analysis indicated complete conversion of starting compound to product. The mixture was allowed to cool and filtered through celite, washing with ethanol. The solvent was removed *in vacuo* to afford a solid which was chromatographed on silica gel with 1% triethylamine in ethyl acetate-petrol (60-80°C) (1:2) as the eluant to yield the ethylthiazolamine (125) as a solid (17.3 g, 63.5%).

Attempted preparation of the ethyltetrahydropyridine (123) using di-imide-1. The ethenyltetrahydropyridine (120) (11 mg, 0.05 mmol) and hydrazine hydrate (0.01 cm^3, 0.25 mmol) were dissolved in a mixture of ethanol (2 cm^3) and methanol (1 cm^3). Into the stirred solution was slurried selenium powder (4 mg, 0.05 mmol) and the mixture was stirred at room temperature in air for several days. The solution was filtered through celite and the solvents removed *in vacuo* to afford an oil. Analysis of the residue revealed a complex mixture; the experiment was therefore abandoned.

Attempted preparation of the ethyltetrahydropyridine (123) using di-imide-2. The ethenyltetrahydropyridine (120) (10 mg, 0.045 mmol) and hydrazine hydrate (0.02 cm^3, 0.45 mmol) were stirred at ice bath temperature in ethanol (5 cm^3). 30% hydrogen peroxide (0.05 cm^3, 0.45 mmol) was added to this solution over 1½h, keeping the temperature of the reaction mixture below 30°C. After this time however t.l.c. analysis revealed a complex mixture of products; the experiment was therefore abandoned.

Attempted preparation of the ethyltetrahydropyridine (123) using di-imide-3. The ethenyltetrahydropyridine (120) (23 mg, 0.9 mmol) was stirred in methanol (10 cm^3) under nitrogen and in this solution was slurried potassium azodicarboxylate

(176 mg, 0.9 mmol) which had been prepared according to the method of Thiele.[21] A solution of acetic acid (0.06 cm^3) in methanol (5 cm^3) was added dropwise to the stirred mixture over a period of ½h. The resulting reaction mixture was stirred at room temperature overnight. Analysis by t.l.c. indicated that the starting material had remained unchanged and hence the experiment was abandoned.

Preparation of the ethyltetrahydropyridine (123) using di-imide-4.- The ethenyltetrahydropyridine (120) (100 mg, 0.45 mmol) and *p*-toluenesulphonhydrazide (2.02 g, 10.9 mmol) were dissolved in ethanol (8 cm^3). The mixture was heated to effect solution and then under gentle reflux. Sodium acetate trihydrate (2.95 g, 21.7 mmol) in water (8 cm^3) was added dropwise over *ca.* 5h, keeping the reaction mixture at reflux temperature during the addition. The resulting solution was allowed to cool, aqueous ammonium chloride was added, the mixture was basified (Na_2CO_3) and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated to afford an oil. This was chromatographed on silica gel with 1% triethylamine in ethyl acetate as eluant to yield the ethyltetrahydropyridine (123) an oil (39 mg, 39%).

Preparation of the ethyltetrahydropyridine (123) using di-imide-5.- The ethenyltetrahydropyridine (120) (200 mg, 0.9 mmol) and 2,4,6-trimethylbenzenesulphonyl hydrazide (MSH) (427 mg, 0.19 mmol) were dissolved in methanol (6 cm^3). The solution was heated under reflux for ½h and t.l.c analysis indicated partial conversion of starting material to product. A further 500 mg of MSH was added and the mixture was heated for 5h. The solution was allowed to cool and the solvents were removed *in vacuo.* The residue was preadsorbed onto silica gel and chromatographed using 1% triethylamine in ethyl acetate as eluant. This resulted in the isolation of ethenyltetrahydropyridine (120) (33 mg) and the ethyl-

tetrahydropyridine (123) (104 mg).

Attempted preparation of the ethyltetrahydropyridine (123) using sodium hydrotelluride.- The ethenyltetrahydropyridine (120) (5 mg, 0.023 mmol) and sodium borohydride (10 mg, 0.27 mmol) were dissolved in ethanol (5 cm^3) and into the stirred, cooled (0°C) solution was slurried tellurium powder (7 mg, 0.06 mmol). The mixture was heated under reflux for 4h, after which time t.l.c. analysis indicated starting material and no product. Heating was continued for an extended period (*ca.* 5h), however still no products appeared and the experiment was abandoned.

Attempted preparation of the ethyltetrahydropyridine (123) using tris(triphenylphosphine)rhodium(I) chloride (Wilkinson's catalyst[22] *).*- The ethenyltetrahydropyridine (120) (30 mg, 0.13 mmol) was dissolved in ethanol (15 cm^3) and this was added to a stirred solution of Wilkinson's catalyst (10 mg, 0.011 mmol) in toluene (15 cm^3). The mixture was hydrogenated overnight at atmospheric pressure and room temperature and then at 4 atmospheres (glass vessel) for several hours. Finally, the stirred solution was heated at 60°C under hydrogen gas at 4 atmospheres. After each stage, t.l.c. analysis indicated the presence only of starting material, and in the latter case base line decomposition material also. The experiment was therefore abandoned.

Preparation of the 2,5,-dimethylpyrrole (129).- The ethylthiazolamine (125) (2 g, 9.8 mmol) and acetonylacetone (1.38 cm^3, 11.7 mmol) were dissolved in toluene (100 cm^3) with acetic acid (2 cm^3) and *p*-toluenesulphonic acid (50 mg). The stirred mixture was heated under reflux in a vessel fitted with a Dean-Stark attachment for 18h. After cooling the solvents were removed *in vacuo*, the residue was taken up in ethyl acetate, washed with sodium carbonate solution followed by brine and dried

($MgSO_4$). The solution was concentrated to afford an oil which was chromatographed on silica gel with ethyl acetate–cyclohexane (1:3) as eluant to yield *4-[2-(2-pyridyl)ethyl]-2-(*N*-2,5-dimethylpyrrolyl)thiazole (129)* [R_F 0.27, ethyl acetate–toluene (1:1)] as an oil, (2.7 g, 99%); $\nu_{max.}$ (film) 2 922 (C–H), 1 711, 1 591, 1 520, 1 488, 1 433, 1 374, 1 296, 1 216, 1 159, 766 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 2.20 (6 H, s, pyrrole CH_3), 3.20 (4 H, s, 1'-H, 2'-H), 5.85 (2 H, s, pyrrole 3-H, 4-H), 6.85 (1 H, s, 5-H), 7.10 (1 H, d, $J_{3'',4''}$ 7.5 Hz, 3''-H), 7.11 (1 H, m, 5''-H), 7.55 (1 H, td, $J_{3'',4''5''}$ 7.5, $J_{4'',6''}$ *ca.* 1 Hz, 4''-H), 8.55 (1 H, dm, $J_{5'',6''}$ 5 Hz, 6''-H); *m/z* (70 eV EI) 283 (M^+, 100%), 268 (23), 189 (49), 134 (46), 130 (41) (Found: M^+, 283.1119. $C_{16}H_{17}N_3S$ requires *M*, 283.1141).

Preparation of the ethyltetrahydropyridine (130). The 2,5-dimethylpyrrole (129) (2 g, 7 mmol) and benzyl bromide (0.84 cm^3, 7 mmol) were dissolved in acetonitrile (25 cm^3) and heated under reflux, with a further addition of benzyl bromide (0.2 cm^3) after 1h. After 2h, t.l.c. analysis indicated that most of the starting material had converted to product, and the reaction mixture allowed to cool and the solvents removed *in vacuo*. The residue was dissolved in ethanol (30 cm^3) and to the stirred solution was added sodium borohydride (500 mg, 14 mmol). After 1h at room temperature, acetone (10 cm^3) was added to destroy any remaining sodium borohydride and the solvents were removed *in vacuo*. Ethyl acetate and 2M HCl were added, and the mixture was basified with sodium carbonate. The aqueous phase was extracted several times with ethyl acetate, the combined organic fractions were washed with brine, dried ($MgSO_4$) and concentrated to afford an oil. This was chromatographed on silica gel with 1% ammonia in methanol–acetone–dichloromethane (2:3:94) as eluant to yield *4-[2-(*N*-benzyl-1,2,3,6-tetrahydropyrid-2-yl)ethyl]-2-thiazolamine (130)* [R_F 0.25, 1% ammonia in methanol–acetone–dichloromethane (2:3:94)] as an oil (204 mg, 10%); $\nu_{max.}$ ($CHCl_3$) 3 450 and 3 360

(N-H), 2 900 (aliphatic C-H), 1 700w, 1 595 (C=C), 1 480, 1 435br, 1 325, 1 130, 1 090, 900 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.73 (1 H, dq, $J_{2',2'(gem)}$ 14.7, J_{vic} 8 Hz, 2'-H), 1.95 (2 H, m, 2'-H, 3''-H), 2.30 (1 H, dm, $J_{3'',3''(gem)}$ 17.5 Hz, 3''-H), 2.60 (2 H, t, $J_{1',2'}$ 8 Hz, 1'-H), 2.85 (1 H, m, 2''-H), 3.00 (1 H, dm, $J_{6'',6''(gem)}$ 17 Hz, 6''-H), 3.10 (1 H, dm, $J_{6'',6''(gem)}$ 17 Hz, 6''-H), 3.63 (1 H, d, J_{gem} 12.5 Hz, C*H*$_2$Ph), 3.71 (1 H, d, J_{gem} 12.5 Hz, C*H*$_2$Ph), 5.18 (2 H, br s, N*H*$_2$), 5.60 (1 H, dm, $J_{4'',5''(cis)}$ 10 Hz, 5''-H), 5.75 (1 H, dm, $J_{4'',5''(cis)}$ 10 Hz, 4''-H), 6.06 (1 H, s, 5-H), 7.20–7.40 (5 H, m, Ph); δ_C (67.8 MHz; $CDCl_3$) 27.6 (t, 2'-C), 28.5 (t, 3''-C), 28.7 (t, 1'-C), 47.9 (t, 6''-C), 55.2 (d, 2''-C), 56.2 (t, *C*H$_2$Ph), 102.2 (d, 5-C), 124.3 (d, 4''-C), 125.0 (d, 5''-C), 126.7 (d, *para*-C), 128.2 (d, *ortho*-C), 128.8 (d, *meta*-C), 139.8 (s, 1-C Ph), 153.3 (s, 4-C), 167.3 (s, 2-C); *m/z* (low eV EI) 299 (M^+, 13%), 208 (100, M-CH_2Ph), 173 (27) (Found: M^+, 299.1433. $C_{17}H_{21}N_3S$ requires M, 299.1454).

Preparation of the phthalimide (131).- The ethylthiazolamine (125) (12 g, 58.5 mmol) and phthalic anhydride (9.6 g, 65 mmol) were dissolved in chloroform (300 cm^3) and this was heated under reflux for *ca.* 5h. After this time t.l.c. analysis (1% triethylamine in ethyl acetate) indicated almost complete conversion of starting compound to product. The solvents were removed *in vacuo* and the resultant oil was chromatographed on silica gel with 1% triethylamine in ethyl acetate-petrol (60–80°C) (1:3) as eluant to yield *4-[2-(2-pyridyl)ethyl]-2-(N-phthalimido)thiazole (131)* (R_F 0.6, solv. 3) as a solid (10 g, 51%), m.p. 134°C (from ethanol) (Found: C, 64.1; H, 3.8; N, 12.4. $C_{18}H_{13}N_3O_2S$ requires C, 64.45; H, 3.9; N, 12.5%); $\nu_{max.}$ ($CHCl_3$) 1 790 and 1 720s (5-ring imide C=O), 1 585, 1 460, 1 425w, 1 340s, 1 120, 875 cm^{-1}; δH (270 MHz; $CDCl_3$) 3.27 (4 H, m, 1'-H, 2'-H), 6.90 (1 H, s, 5-H), 7.11 (1 H, ddd, $J_{4'',5''}$ 8, $J_{5'',6''}$ 5, $J_{3'',5''}$ 1 Hz, 5''-H), 7.16 (1 H, d, $J_{3'',4''}$ 8 Hz, 3''-H), 7.57 (1 H, td, $J_{3'',4'',5''}$ 8, $J_{4'',6''}$ 2 Hz, 4''-H), 7.82 (2 H, dd, $J_{\beta,\gamma}$ 5.5, $J_{\beta',\gamma}$ 3 Hz, γ, γ'-H), 7.98 (2 H, dd, $J_{\beta,\gamma}$ 5.5, $J_{\beta,\gamma'}$ 3 Hz, β, β'-H), 8.55 (1 H, d, $J_{5'',6''}$ 5 Hz, 6''-H); δ_C (67.8 MHz; $CDCl_3$) 31.3

(t, 1'-C), 37.1 (t, 2'-C), 112.8 (d, 5-C), 121.0 (d, 5''-C), 122.9 (d, 3''-C), 124.1 (d, β, β'-C), 131.0 (s, α, α'-C), 134.9 (d, γ, γ'-C), 136.2 (d, 4''-C), 149.0 (d, 6''-C), 150.9 (s, 4-C), 153.6 (s, 2-C), 160.6 (s, 2''-C), 164.6 (s, *C*=O); *m/z* (isobutane CI) 336 (*M+1*, 90%), 246 (30).

Preparation of the phthalimido benzyl bromide (132).- The phthalimide (131) (5.68 g, 17 mmol) and benzyl bromide (2.9 g, 17 mmol) were dissolved in acetonitrile (100 cm^3) and heated under reflux for 3h, and then stirred at room temperature overnight. The solvents were removed *in vacuo* and the mixture was chromatographed on alumina with 2-propanol-ethyl acetate (1:3). This resulted in the isolation of an unidentified orange glass (5.11 g, R_F 0.65, solv. 4). Increased eluant polarity eventually yielded *4-{2-[2-(N-benzyl)pyridinium]ethyl}-2-(N-phthalimido)thiazole bromide (132)* (R_F 0.4, solv. 4) as a grey solid (1.32 g, 15.3%) m.p. 205-215°C (decomp.); δ_H [270 MHz; $(CD_3)_2SO$] 3.03 (2 H, t, $J_{1',2'}$ 7.5 Hz, 1'-H), [3.45 (2 H, t, $J_{1',2'}$ 7.5 Hz, 2'-H), obscured by peak due to H_2O], 6.08 (2 H, s, C*H*$_2$Ph), 6.82 (1 H, s, 5-H), 7.31-7.55 (7 H, m, Ph, γ and γ'-H), 7.85 (1 H, dd, $J_{\beta,\gamma}$ 7.5, $J_{\beta,\gamma'}$ 1.5 Hz, β-H), 7.98 (1 H, dd, $J_{\beta',\gamma'}$ 7.5, $J_{\beta',\gamma}$ 1.5 Hz, β'-H), 8.10 (2 H, m, 3''-H, 5''-H), 8.62 (1 H, td, $J_{3'',4'',5''}$ 7.5, $J_{4'',6''}$ 1 Hz, 4''-H), 9.25 (1 H, d, $J_{5'',6''}$ 5.25 Hz, 6''-H).

Preparation of the ethyltetrahydropyridine (133).- The phthalimido benzyl bromide (132) (1 g, 1.9 mmol) was slurried in ethanol (40 cm^3) and to the cooled (0°C) mixture was added sodium borohydride (151 mg, 4 mmol). The resultant solution was allowed to warm to room temperature for 1h, and acetone was added to quench excess sodium borohydride. The solvents were removed under reduced pressure and ethyl acetate and 2M HCl were used to dissolve the residue. The mixture was basified (Na_2CO_3) and the organic layer was separated. The aqueous phase was extracted (EtOAc × 3), the combined organic extracts were washed with brine, dried

($MgSO_4$) and the solvents were removed *in vacuo* to afford a solid. This was chromatographed on silica gel with 1% ammonia in methanol–acetone–chloroform (3:5:92) as eluant to yield *4-[2-(N-benzyl-1,2,3,6-tetrahydropyrid-2-yl)ethyl]-2-(N-phthalimido)thiazole* (133) (R_F 0.25, solv. 5) as a solid (350 mg, 43%), m.p. 175–177°C (Found: C, 69.7; H, 5.5; N, 9.7. $C_{25}H_{23}N_3O_2S$ requires, C, 69.9; H, 5.4; N, 9.8%); $\lambda_{max.}$ (EtOH) 201, 293 nm; $\nu_{max.}$ (nujol) 1 651, 1 540, 1 460, 1 370, 1 300, 900, 835, 750, 700, 660 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.76 (1 H, dq, $J_{2',2''}$ 15, J 8 Hz, 2'–H), 1.95 (1 H, dm, $J_{3'',3''}$ 18 Hz, 3''–H), 2.05 (1 H, m, 2'–H), 2.30 (1 H, dm, $J_{3'',3''}$ 18 Hz, 3''–H), 2.71 (2 H, t, $J_{1',2'}$ 8 Hz, 1'–H), 2.93 (1 H, m, 2''–H), 3.00 (1 H, dm, $J_{6'',6''}$ 18 Hz, 6''–H), 3.12 (1 H, dm, $J_{6'',6''}$ 18 Hz, 6''–H), 3.67 and 3.75 (2 H, convergent dd, J_{gem} 11 Hz, C*H*$_2$Ph), 5.60 (1 H, dm, $J_{4'',5''}$ 10 Hz, 5''–H), 5.76 (1 H, dm, $J_{4'',5''}$ 10 Hz, 4''–H), 6.50 (1 H, s, 5–H), 7.2–7.4 (5 H, m, Ph), 7.44 (1 H, td, J 7.3, J 1.7 Hz, γ–H), 7.50 (1 H, td, J 7.3, J 1.7 Hz, γ'–H), 7.83 (1 H, dd, J 7.3, J 1.7 Hz, β–H), 8.22 (1 H, dd, J 7.3, J 1.7 Hz, β'–H); *m/z* (isobutane CI) 430 (*M+1*, 2%), 300 (50), 208 (25), 149 (100), 102 (56), 101 (33), 86 (36).

Preparation of the methiodide (134). The phthalimide (131) (150 mg, 0.6 mmol) was dissolved in acetonitrile (10 cm^3) and this was heated to reflux with stirring. Iodomethane (*ca.* 2 cm^3) was added to the solution in small portions, and heating was continued for 3h. On cooling, the product crystallised out and the solvent was removed under reduced pressure. The resulting solid was recrystallised from ethanol–methanol to yield *4-{2-[2-(N-methyl)pyridinium]ethyl}-2-(N-phthalimido)thiazole iodide* (134) (R_F 0.4, solv. 4) as a yellowish solid (160 mg, 75%), m.p. 205–207°C; (Found: C, 47.7; H, 3.3; N, 8.8. $C_{19}H_{16}IN_3O_2S$ requires, C, 47.8; H, 3.4; N, 8.8%); $\nu_{max.}$ (nujol) 3 080, 3 040, 1 790 and 1 720vs (5–ring imide C=O), 1 630, 1 575w, 1 355vs, 1 335vs, 1 275, 1 225, 1 180, 1 160, 1 130s, 1 045, 885, 785, 760, 715s cm^{-1}; δ_H [270 MHz; $(CD_3)_2SO$] 3.32 (2 H, t, $J_{1',2'}$ 7 Hz, 1'–H), 3.55 (2 H,

t, $J_{1',2'}$ 7 Hz, 2'-H), 4.35 (3 H, s, CH_3), 7.55 (1 H, s, 5-H), 7.99 (5 H, m, 5''-H, phthalimide-H), 8.08 (1 H, d, $J_{3'',4''}$ 8 Hz, 3''-H), 8.51 (1 H, t, $J_{3'',4'',5''}$ 8 Hz, 4''-H), 9.03 (1 H, d, $J_{5'',6''}$ 6 Hz, 6''-H); δ_C [67.8 MHz; $(CD_3)_2SO$] 28.3 (t, 1'-C), 31.2 (t, 2'-C), 45.6 (q, *C* H_3), 115.4 (d, 5-C), 124.0 (d, β,β'-C), 125.4 (d, 5''-C), 128.2 (d, 3''-C), 131.0 (s, α,α'-C), 135.4 (d, γ,γ'-C), 145.0 (d, 6''-C), 146.5 (d, 4''-C), 150.6 (s, 4-C), 151.5 (s, 2-C), 157.6 (s, 2''-C), 165.0 (s, *C* =O).

Sodium borohydride reduction of the methiodide (134).- The methiodide (134) (12.4 g, 26 mmol) was dissolved in ethanol (100 cm^3) and the stirred solution was cooled to 0°C. Sodium borohydride (2.27 g, 60 mmol) was added and the reaction mixture was allowed to warm to room temperature over 1h. The solvents were removed *in vacuo*, the residue was successively acidified (2 M HCl) and basified (Na_2CO_3/ NaOH solution) and finally extracted with ethyl acetate. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated. Analysis by t.l.c. indicated however that the organic extract contained no products. The aqueous phase was therefore mixed with 2-propanol and concentrated *in vacuo* to afford an oil. This was chromatographed on silica gel with 1% ammonia in methanol-chloroform (1:19) to yield *4-[2-(*N*-methyl-1,2,5,6-tetrahydropyrid-2-yl)ethyl]-2-thiazolamine* (135) (R_F 0.45, solv. 5) and *4-[2-(*N*-methyl-1,2,3,6-tetrahydropyrid-2-yl)ethyl]-2-thiazolamine* (123) as a 1:3 mixture (1 g, 17%). Using preparative centrifugally accelerated thin layer radial chromatography, the ethyltetrahydropyridine (135) was isolated as an oil (294 mg, 5%), $\nu_{max.}$ ($CHCl_3$) 3 477 and 3 407 (N-H), 3 020s (C-H), 1 600 (C=C), 1 510 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.87 (2 H, m, 2'-H), 2.00 (1 H, dm, $J_{5'',5''(gem)}$ 16.5 Hz, 5''-H), 2.27 (1 H, m, 5''-H), 2.36 (3 H, s, CH_3), 2.43 (1 H, m, 6''-H), 2.52 (1 H, dd, *J* 10, *J* 6 Hz, 1'-H), 2.62 (1 H, dd, *J* 10, *J* 6 Hz, 1'-H), 2.72 (1 H, m, 2''-H). 2.87 (1 H, ddd, $J_{6'',6''}$ 12, $J_{5'',6''}$ 5, $J_{5'',6''}$ 4 Hz, 6''-H), 5.12-5.22 (2 H, br s, NH_2), 5.58 (1 H, dm, J_{cis} 10 Hz, 3''-H), 5.80 (1 H, dm, J_{cis} 10 Hz,

4'' H), 6.09 (1 H, s, 5-H); δ_C (67.8 MHz; $CDCl_3$) 24.9 (t, 2'-C), 27.0 (t, 5''-C), 31.7 (t, 1'-C), 43.0 (q, *C* H_3), 51.3 (t, 6''-C), 61.3 (d, 2''-C), 101.9 (d, 5-C), 125.4 (d, 4''-C), 129.2 (d, 3''-C), 152.5 (s, 4-C), 168.2 (s, 2-C); *m/z* (isobutane CI) 224 (*M+1*, 100%), 223 (59), 222 (25), 109 (25), 96 (82) (Found: M^+, 223.1136. $C_{11}H_{17}N_3S$ requires *M*, 223.1142). The ethyltetrahydropyridine (123) was also isolated (706 mg, 12%) with spectral data identical to those previously recorded.

Preparation of the fumarate (122).- Fumaric acid (184 mg, 1.6 mmol) in methanol (10 cm^3) was dripped into a stirred solution of the ethenyltetrahydropyridine (120) (700 mg, 3.17 mmol) in methanol (10 cm^3) at room temperature. After ½h, the solvent was removed under reduced pressure and the solid residue was crystallised from methanol-ether to yield the fumarate salt (122) in 2 crops, (1 st crop: 700 mg, purity 95.3% by g.l.c. 2nd crop: 190 mg, purity 93% by g.l.c). These were combined, dissolved in methanol, filtered through charcoal and the solvents again removed *in vacuo* to afford a solid which was recrystallised from methanol-ether to give *4-[2-(N-methyl-1,2,3,6-tetrahydropyrid-2-yl)ethenyl]-2-thiazolamine fumarate (122)* (R_F 0.41, solv. 5) as colourless crystals (700 mg, 79%, purity 96.9% by g.l.c.); m.p. 209°C (decomp.) (Found: C, 55.9; H, 6.1; N, 15.0; S, 11.6. $C_{13}H_{17}N_3O_2S$ requires C, 55.75; H, 6.2; N, 14.9; S, 11.3%.) $\lambda_{max.}$ (EtOH) 220 (ϵ 30 416 dm^3 mol^{-1} cm^{-1}), 268 nm (12 355); $\nu_{max.}$ (KCl) 3 300s and 3 108vs (O-H, N-H), 1 654, 1 590vs, 1 533vs, 1 452, 1 375vs, 1 127, 1 019, 968s, 709, 664, 562, 527, 440 cm^{-1}; δ_H [200 MHz; $(CD_3)_2SO$] 2.10 (2 H, dm, $J_{3'',3''(gem)}$ 18 Hz, 3''-H), 2.25 (3 H, s, C*H* $_3$), 3.00 (1 H, br d, $J_{6'',6''(gem)}$ 18 Hz, 6''-H), 3.15 (2 H, m, 2''-H, 6''-H), 5.70 (2 H, convergent pair of d, $J \approx$ 11 Hz, 4''-H, 5''-H), 6.12 (1 H, dd, $J_{1',2'}$ 14.3, $J_{2',2'}$ 7 Hz, 2'-H), 6.33 (1 H, d, $J_{1',2'}$ 14.3 Hz, 1'-H), 6.45 (1 H, s, 5-H), 6.55 [1 H, s, $(^-O_2CCH =)_2$], 7.05 (3 H, br s, N^+H_3).

7.6 Experimental to Chapter 6.

Attempted oxidative coupling reaction.- The ethylisoxazole (83) (25 mg, 0.1 mmol) and palladium acetate (25 mg, 0.11 mmol) were dissolved in trifluoroacetic acid (10 cm^3) and heated under reflux for several hours. Analysis by t.l.c. during this time indicated a diminution of starting material as well as base line decomposition products. A trace of iodine was added and heating was continued. The solvents were removed *in vacuo*, the residue taken up in diethyl ether and washed with sodium carbonate solution, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel with ethyl acetate-petrol (60-80°) (1:1) as eluant to yield recovered starting material (8 mg).

Preparation of the bromothiazolamine (141).- The bromodienone (142) (41 mg, 0.1 mmol) in dichloromethane (1 cm^3) was added to the ethylthiazolamine (125) (20 mg, 0.1 mmol) in dichloromethane (4 cm^3) at -50°C. This was allowed to warm to -20°C over ½h before sodium carbonate solution was added. The mixture was extracted with ethyl acetate, the organic phase was washed with brine, dried ($MgSO_4$), and concentrated to an oil. Analysis by t.l.c. indicated that a new compound had formed and the oil was chromatographed on silica gel with 1% triethylamine in ethyl acetate as eluant to yield *5-bromo-4-[2-(2-pyridyl)ethyl]-2-thiazolamine* (141) as a gum (16 mg, 56%); $\nu_{max.}$ (nujol) 3 240 and 3 080 (N-H), 1 620, 1 580w, 1 520, 1 290w, 1 150w, 1 020, 990, 760 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 2.78 (2 H, m, 1'-H), 2.97 (2 H, m, 2'-H), 7.20 (2 H, br s, NH_2), 7.20 (1 H, d, $J_{3'',4''}$ 7.4 Hz, 3''-H), 7.20 (1 H, m, 5''-H), 7.70 (1 H, td, $J_{3'',4'',5''}$ 7.4, $J_{4'',6''}$ 1 Hz, 4''-H), 8.49 (1 H, dm, $J_{5'',6''}$ 4.7 Hz, 6''-H); *m/z* (isobutane CI) 286 [*M+1* (^{81}Br), 14%], 284 [*M+1* (^{79}Br), 14], 204 (*M* − Br, 100), 149 (31).

Attempted epoxidation/ring opening with bromine-sodium bromide solution.- The ethyl tetrahydropyridine (123) (380 mg, 1 mmol) was stirred in diethyl ether (10 cm^3) and through this solution was bubbled hydrogen bromide gas for a few minutes. The diethyl ether was removed *in vacuo* and the residue was dissolved in water (3 cm^3). To the stirred solution of the hydrobromide was added a solution of sodium bromide (258 mg, 2.5 mmol) and bromine (0.05 cm^3) in water (2 cm^3) over ½h. To the cooled (ice–methanol bath) reaction mixture was added a cold solution of 4M sodium hydroxide solution (3 cm^3) dropwise over a period of 5 minutes. The mixture was stirred for ½h, extracted with ethyl acetate, the organic phase was dried ($MgSO_4$) and the solvents removed *in vacuo*. Chromatography [silica gel with 1% ammonia in methanol-acetone–chloroform (2:3:94) as eluant] resulted in the recovery of a trace of starting material (6 mg).

Attempted epoxidation of the ethyltetrahydropyridine (133) with m-*CPBA.*- The ethyltetrahydropyridine (133) (50 mg, 0.12 mmol) was dissolved in dry dichloromethane (10 cm^3) and to this was added *m*-CPBA (23 mg, 0.13 mmol) with stirring. After 1h, t.l.c. analysis indicated the possible presence of a lower running compound than starting material, and sodium sulphite was added. The mixture was basified (Na_2CO_3 solution), extracted with dichloromethane and the organic phase dried ($MgSO_4$). After the solvents were removed *in vacuo*, the residue was chromatographed on silica gel with 1% ammonia in methanol–acetone–chloroform (2:3:94) as eluant. No products were isolated, however, and the experiment was abandoned.

Attempted "Grewe"-type cyclisation of the ethyltetrahydropyridine (123).- The ethyltetrahydropyridine (123) (100 mg, 0.5 mmol) was heated under reflux in 48% aqueous hydrobromic acid (5 cm^3) for several hours, the reaction being monitored by t.l.c. analysis. Once the starting material had disappeared, the reaction

mixture was cooled, basified (Na_2CO_3, NaOH solution) and 2-propanol was added. The solvents were removed *in vacuo* azeotropically to yield a residue containing the starting compound (123) (20 mg) and decomposition material.

Attempted cyclisation of the ethylthiazolamine (135) with a Ag^+-Pd^{2+} mixed metal system.[23, 24] - Dry, crystalline silver tetrafluoroborate (66 mg, 0.34 mmol) and palladium chloride (60 mg, 0.34 mmol) were stirred together in dry acetonitrile (5 cm^3) for 1h under nitrogen. This resulted in the formation of a silver grey suspension of metal salts in a yellow solution. The ethylthiazolamine (135) (36 mg, 0.16 mmol) in acetonitrile (2 cm^3) was added *via* a syringe and this was stirred at room temperature overnight. [The solution turned dark red on addition of the ethylthiazolamine (135)] Ethanol (7 cm^3) was added, the mixture was chilled (ice-methanol bath) and sodium borohydride (10 mg) was added over ½h. The mixture was stirred at room temperature for a further ½h and then allowed to warm to room temperature over ½h. The solvents were removed *in vacuo*, the residue was acidified (2 M HCl), basified (Na_2CO_3) and 2-propanol was added. The solvents were removed *in vacuo* azeotropically and chromatographed on silica gel with 1% ammonia in acetone-ethanol-chloroform (5:7:87) to yield a trace of starting material (5 mg) and no other discernible products.

Preparation of the thiazolacetamide (161).- 2-Thiazolacetamide (158) (426 mg, 3 mmol), styrene (154) (0.34 cm^3, 3 mmol), palladium acetate (112 mg, 0.5 mmol) and copper II acetate (1.2 g, 6 mmol) were dissolved in acetic acid (20 cm^3) and the mixture was heated under reflux for 8h. After this time the reaction mixture was allowed to cool, the acetic acid was removed *in vacuo* and water (15 cm^3), ethyl acetate (15 cm^3), ethanolamine (1 cm^3) and sodium carbonate were added. The aqueous layer was extracted with ethyl acetate, dried ($MgSO_4$) and concentrated.

The residue was chromatographed on silica gel with ethyl acetate–petrol (60–80°C) as eluant to yield *5-(1-phenylethenyl)-2-thiazolacetamide* (161) (190 mg, 30%), m.p. 174–176°C; $\lambda_{max.}$ (EtOH) 204 (ϵ 12 470 $dm^3\ mol^{-1}\ cm^{-1}$), 248 (7 540), 297 nm (8 640); $\nu_{max.}$ ($CHCl_3$) 2 410, 2 180, 2 930, 2 850, 1 690 (amide 1), 1 550br, 1 370, 1 290, 1 170w, 1 000, 980, 900, 870 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 2.26 (3 H, s, NHCOC*H*$_3$), 5.30 (1 H, s, C*H*$_2$), 5.54 (1 H, s, C*H*$_2$), 7.18 (1 H, s, N*H* $COCH_3$), 7.40 (6 H, m, 4-H, Ph); δ_C (67.8 MHz; $CDCl_3$) 23.2 (q, NHCO*C* H_3), 115.0 (t, *C* H_2), 126.5 (s, 5-C), 126.7 (d, 4''-C), 128.1 (d, 2''-C_2), 128.4 (d, 3''-C_2), 134.8 (d, 4-C), 140.1 (s, 1''-C), 140.6 (s, 1'-C), 159.2 (s, 2-C), 168.0 (s, *C* OMe); *m/z* (low eV EI) 244 (M^+, 100%), 202 (39), 149 (21) (Found: M^+, 244.067. $C_{13}H_{12}N_2OS$ requires *M*, 244.0669).

Preparation of the amide (162).– The ethylthiazolamine (135) (60 mg, 0.27 mmol) was dissolved in dry acetonitrile (5 cm^3) and to this was added acetic anhydride (0.03 cm^3, 0.3 mmol). The mixture was heated under reflux for ½h, and after this time t.l.c. analysis indicated almost total conversion of starting material to the acylated product. A further equivalent of acetic anhydride was added, and after a further ½h of heating the mixture was allowed to cool, and triethylamine (1 cm^3) was added. The solvents were removed *in vacuo* and the residue was chromatographed on silica gel with 1% ammonia in acetone–ethanol–chloroform (5:7:87) to yield *4-[2-(N-methyl-1,2,5,6-tetrahydropyrid-2-yl)ethyl]-2-thiazolacetamide* (162) (R_F 0.5, solv. 5) as a gum (63 mg, 88%); $\nu_{max.}$ ($CHCl_3$) 3 407 (N-H), 2 920 (C-H), 2 795, 1 676s, 1 540br, 1 365, 1 280s, 1 130, 1 000 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.87 (2 H, m, 2'-H), 2.05 (1 H, m, 5''-H), 2.23 (3 H, s, NHCOC*H*$_3$), 2.25 (1 H, m, 5''-H), 2.32 (3 H, s, NC*H*$_3$), 2.40 (1 H, m, 6''-H), 2.62 (1 H, m, 1'-H), 2.73 (2 H, m, 2''-H, 1'-H), 2.85 (1 H, ddd, $J_{6',6''}$ 11.5, $J_{5',6''}$ 6, $J_{5',6'}$ 3 Hz, 6''-H), 5.54 (1 H, dm, $J_{3'',4''}$ 10.5 Hz, 3''-H), 5.80 (1 H, m, 4''-H), 6.50 (1 H, s, 5-H), 7.20 (1 H, br s, N*H* COMe); δ_C (67.8 MHz; $CDCl_3$) 23.1 (q, CO*C* H_3), 25.0 (t, 2'-C), 26.6 (t, 5''-C), 31.9 (t, 1'-C), 43.1 (q,

N*C* H_3), 51.4 (t, 6''-C), 61.2 (d, 2''-C), 107.3 (d, 5-C), 125.7 (d, 4''-C), 129.1 (d, 3''-C), 151.6 (s, 4-C), 158.2 (s, 2-C), 167.9 (s, NH*C* OMe); *m/z* (low eV EI) 265 (M^+, 52%), 250 (13), 110 (18), 96 (100) (Found: M^+, 265.123. $C_{13}H_{19}N_3OS$ requires *M*, 265.127).

References.

1. D. D. Perrin, W. L. F. Armarego, and D. R. Perrin, *Purification of Laboratory Chemicals,* Pergamon, Oxford (1980).
2. *Dying Reagents for Thin Layer and Paper Chromatography,* E. Merck, Darmstadt, W. Germany (1978).
3. K. W. Wischmann, A. V. Logan, and D. M. Stuart, *J. Org. Chem.*, 1961, **26**, 2794.
4. J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1952, 1094.
5. E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 1975, **16**, 2647.
6. W. M. Coates and J. R. Corrigan, *Chem. Ind.*, 1969, 1594.
7. L. F. Fieser and M. Fieser, *Reagents for Organic Chemistry (Wiley, 1969)*, **2**, 363.
8. K. E. Pfitzner and J. G. Moffatt, *J. Am. Chem. Soc.*, 1965, **87**, 5670.
9. S. L. Huang, K. Omura, and D. Swern, *J. Org. Chem.*, 1976 , **41**, 3329.
10. W. J. Balfour, C. C. Greig, and Somyong Visaisouk, *J. Org. Chem.*, 1974, **39**, 725.
11. M. G. Veliev and M. M. Guseinov, *Synthesis*, 1980, 461.
12. J. C. Sauer, *Org. Synth. Coll. Vol. 4*, 1963 , 813.

13. I. T. Hogan and M. Sainsbury, *Tetrahedron*, 1984, **40**, 681.

14. Kou-Chang Liu, B. R. Shelton, and R. K. Howe, *J. Org. Chem.*, 1980, **45**, 3916.

15. M. Freri and G. S. Skinner, *J. Am. Chem. Soc.*, 1924, **46**, 731.

16. B. I. Rosen and W. P. Weber, *J. Org. Chem.*, 1977, **42**, 47.

17. V. H. Rawal, R. J. Jones, and M. P. Cava, *Tetrahedron Lett.*, 1985, **26**, 2423.

18. F. Benington, R. D. Morin, and M. A. Khaled, *Synthesis*, 1984, 619.

19. R. F. Hudson and P. A. Chopard, *J. Org. Chem.*, 1963, **28**, 2446.

20. S. F. Dyke and M. Sainsbury, *Tetrahedron*, 1967, **23**, 3161.

21. J. Thiele, *Liebigs Ann. Chem*, 1892, **271**, 127.

22. A. J. Birch and K. A. M. Walker, *Tetrahedron Lett.*, 1967, **8**, 1935.

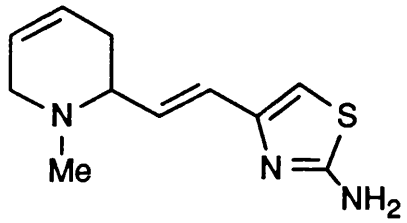
23. B. M. Trost, S. A. Godleski, and J. P. Genet, *J. Am. Chem. Soc.*, 1978, **100**, 3930.

24. B. M. Trost and J. M. D. Fortunak, *Organometallics*, 1982, **1**, 7.

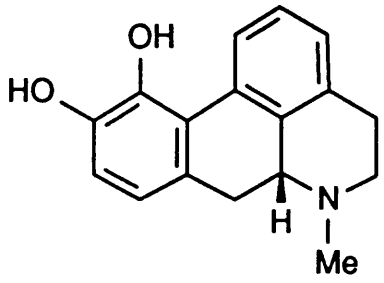
APPENDICES.

A.1 Biological Screening.

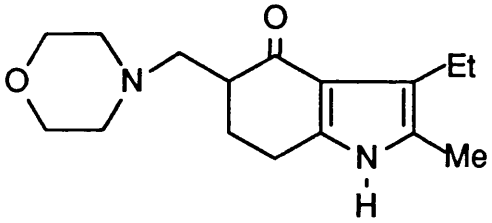
An examination of the structure of the ethenyltetrahydropyridine (120, fig. a.1) reveals that it is similar to known dopaminergically active compounds (see section 1.4). Thus one may assume that within the receptor site the tetrahydropyridine *N*-atom might correspond to the primary amino function of the natural substrate DA (3), whilst the 2-thiazolamine fragment could correlate with the hydroxyphenyl moiety of DA. In fig. a.2 the structures of (120) and DA (3), and also (120) and molindone (30) are superimposed to indicate possible correlations.



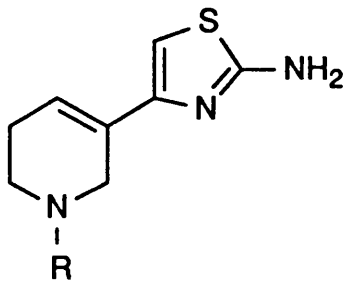
(120)



(9)



(30)



(29)

29a. R=Me

Fig a.1.

The ethenyltetrahydropyridine (120) was submitted for biological testing as the fumarate salt (122, see scheme 5.6). The following screens were employed:

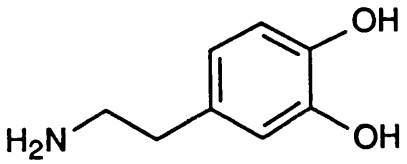
1. Rabbit Ear Artery (REA).-This is an isolated tissue test whereby a DA agonist

will relax tissue contracted by electrical stimulus.

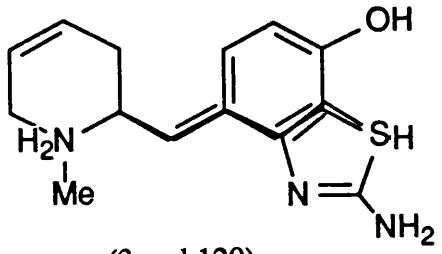
2. Mouse Ambulation (LMAM).–An *in vivo* test whereby DA agonists cause sedation in mice.

3. *N*–Propyl apomorphine binding assay (^{3}H–NPA).– This *in vitro* assay measures the ability of a dopamine agonist to displace ^{3}H–NPA from DA receptors isolated from rat brain striatal membrane homogenates.

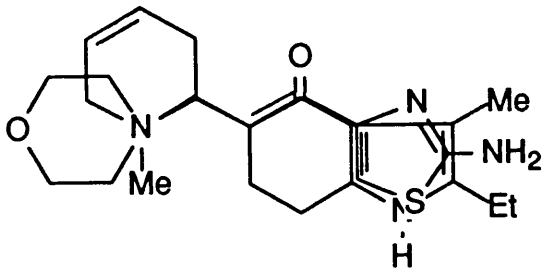
4. Circling Rat Model (CRM).–A particularly sensitive *in vivo* test in which a DA agonist will cause rats to rotate after pretreatment with the neurotoxin 6–hydroxy dopamine to one side of the brain.



(3)



(3 and 120)



(30 and 120)

Fig. a.2.

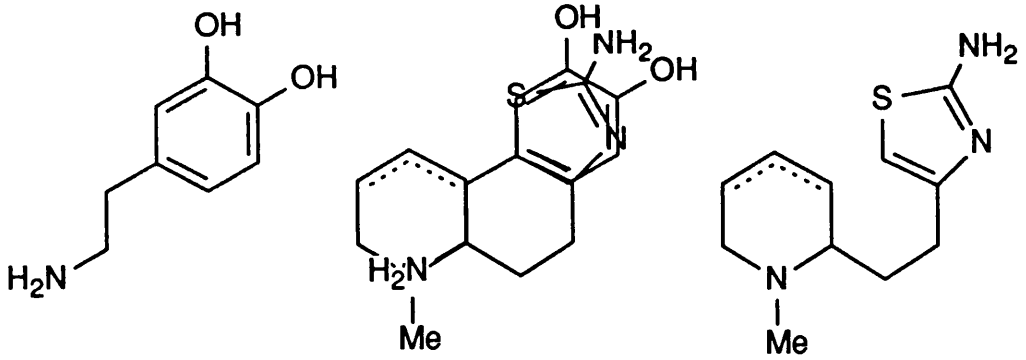
The results of the tests are presented in table a.1. The results for apomorphine (9) and the 2-thiazolamine (29a, fig. a.1) are also included for comparison. They indicate that there is no activity in the NPA and REA tests, but some activity in the LMAM test which, however, may not be mediated through dopaminergic receptors. There is also some weak activity in the circling rat model.

Further investigation of the biological activity of this and other compounds is

worthwhile, since there is a strong possibility that they may show *in vivo* potency by some other mechanism, such as 5-HT antagonism. For example, there is a clear structural similarity between the ethenyltetrahydropyridine (120) and the DA antagonist molindone (30,figs. a.1 and a.2). Thus, the DA antagonistic properties of our compound cannot be ruled out. Also, there is a similarity between DA and the fully reduced compounds (*e.g.* 123 and 135, fig. a.3) and these may well prove to be active (see superimpositions in fig. a.3).

Results of Biological Screening.				
Cpd.	NPA (pKi)	LMAM ED_{50} (mg/kg)	REA IC_{50} (μM)	CRM Threshold Dose (mg/kg)
(9)	8.1	0.1	1.1	0.2
(29a)	7.2	0.5	4.6	0.1
(122)	<5.2	-83% @ 22 mg/kg.	>100	≈22

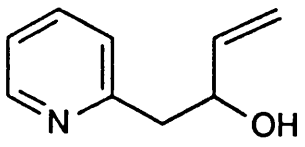
Table a.1.



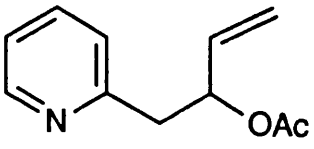
(3) (123, 135 and 3) (123 and 135)

Fig. a.3.

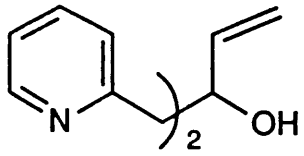
A.2 Structures of Compounds Referred to in Discussion and Experimental.



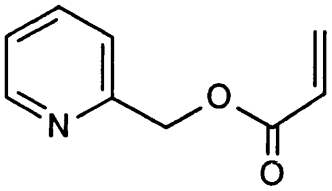
(56)



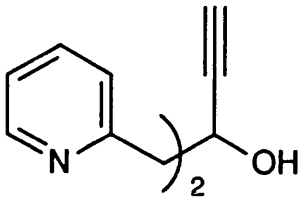
(57)



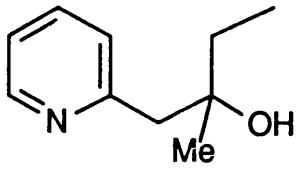
(58)



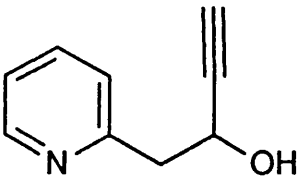
(62)



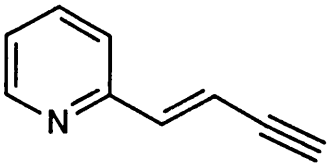
(65)



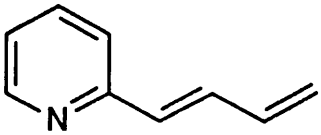
(70)



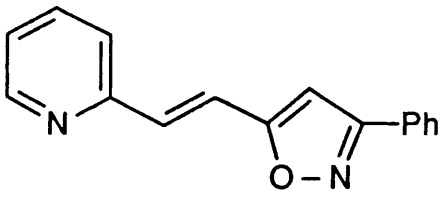
(68)



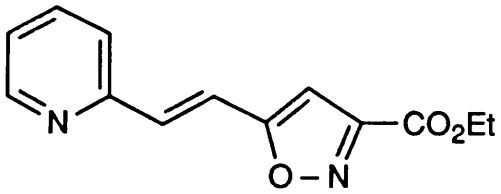
(48)



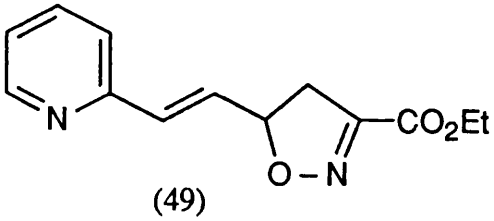
(50)



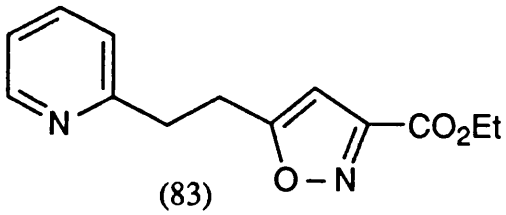
(76)



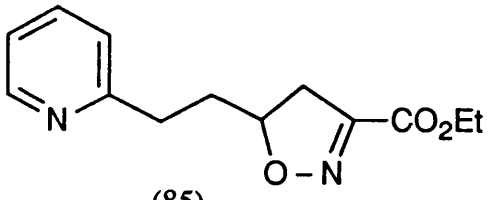
(45)



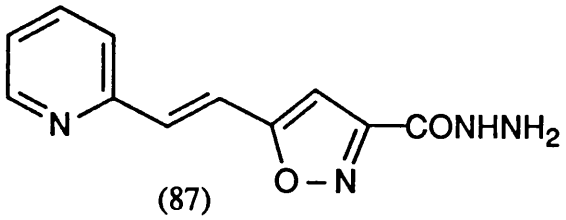
(49)



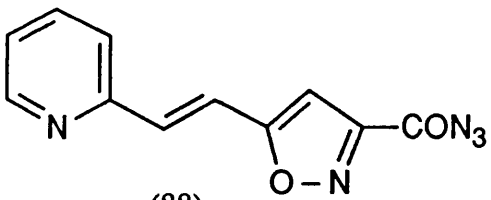
(83)



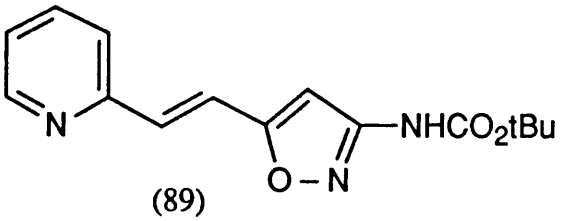
(85)



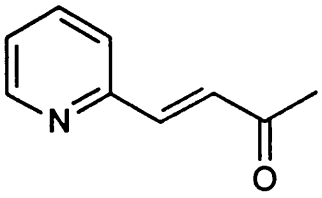
(87)



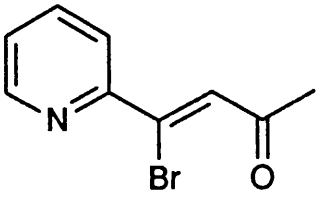
(88)



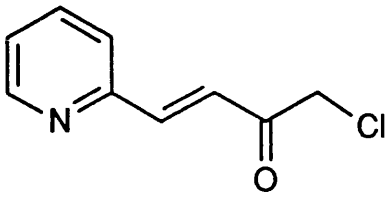
(89)



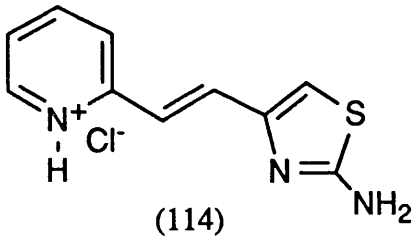
(105)



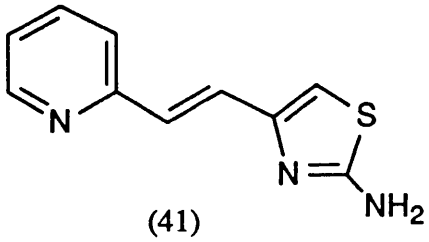
(109)



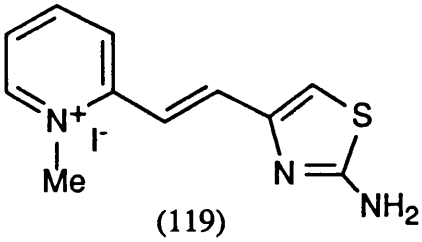
(113)



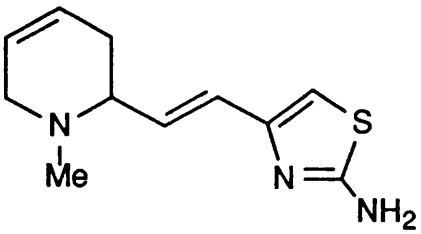
(114)



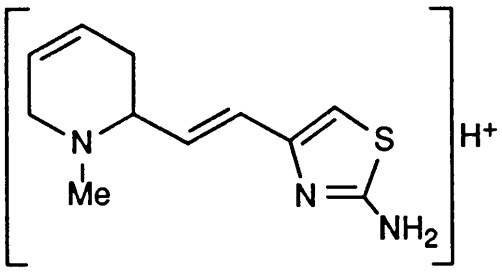
(41)



(119)

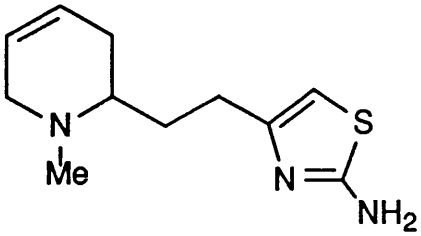


(120)

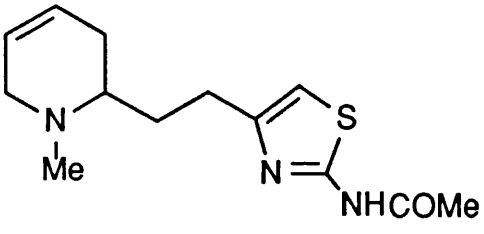


.1/2 (=CHCO$_2^-$)$_2$

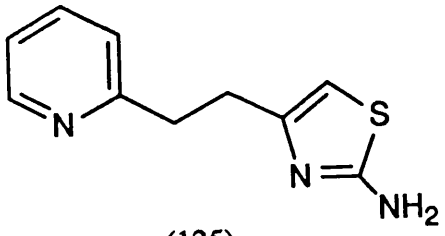
(122)



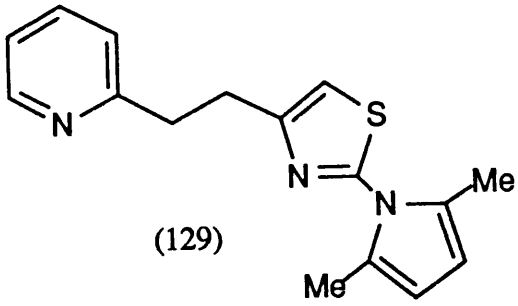
(123)



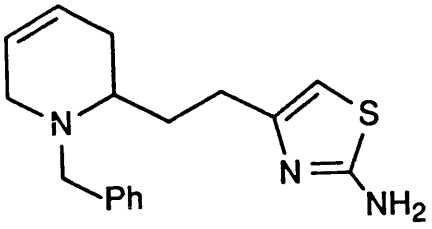
(124)



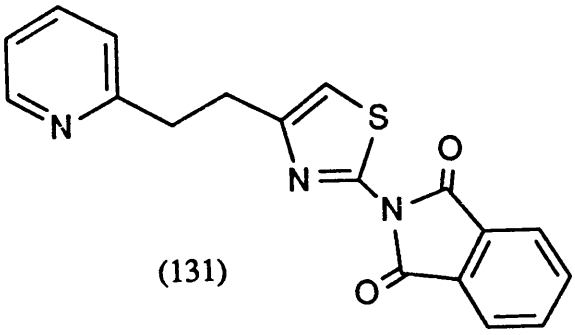
(125)



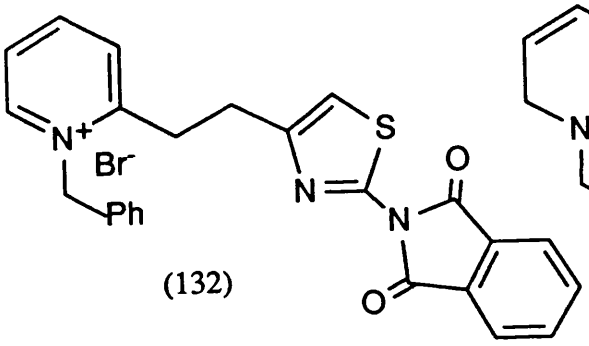
(129)



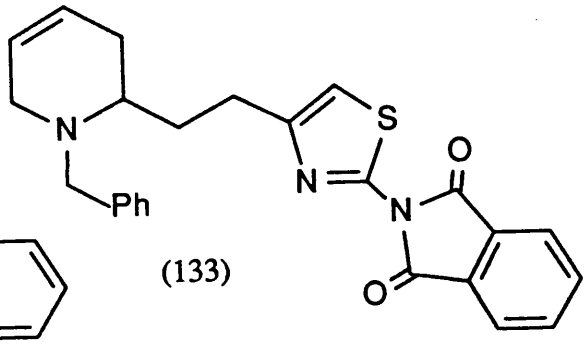
(130)



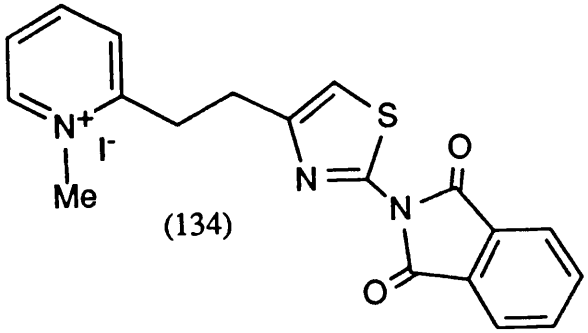
(131)



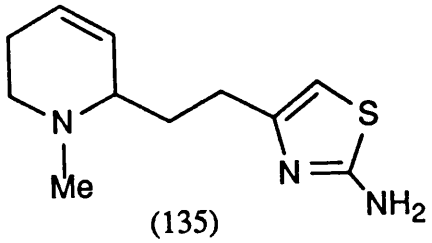
(132)



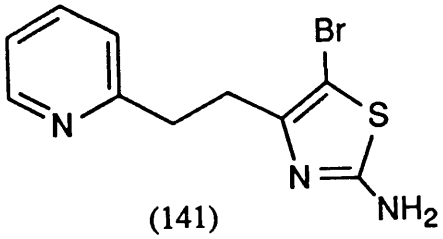
(133)



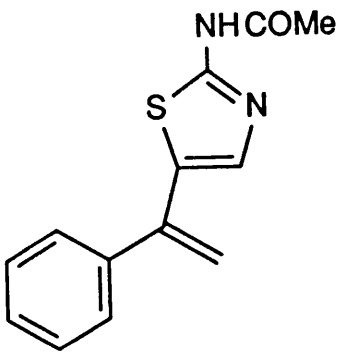
(134)



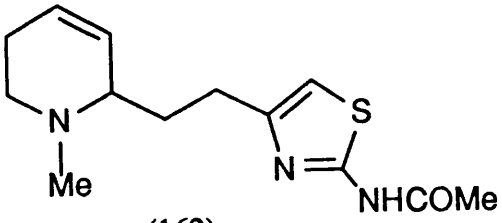
(135)



(141)

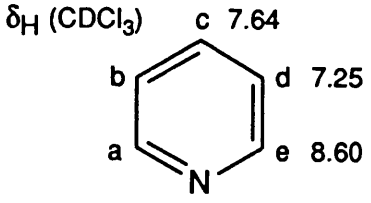


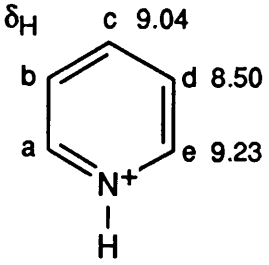
(161)



(162)

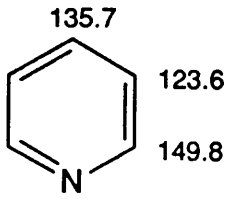
A.3 Literature n.m.r. Data.



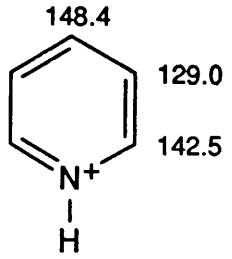


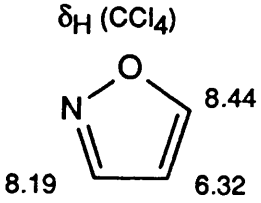
J_{ab} 4-6	J_{ae} 0-0.6
J_{ac} 0-2.5	J_{bc} 7-9
J_{ad}	J_{bd} 0.5-2.0

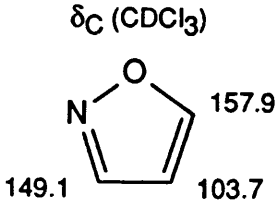
J_{ab} 6.0	J_{ae} 1.0
J_{ac} 1.5	J_{bc} 8.0
J_{ad} 0.8	J_{bd} 1.4

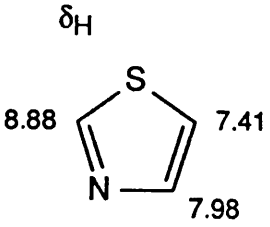


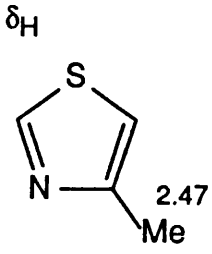
δ_C Base line values.

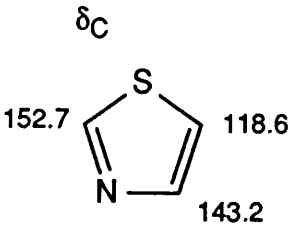


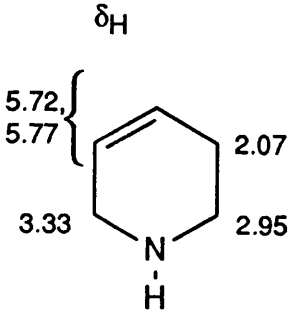


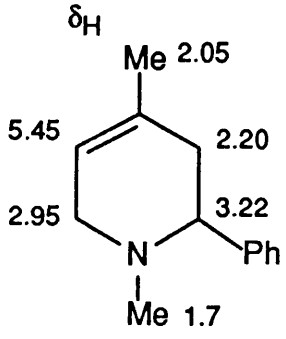


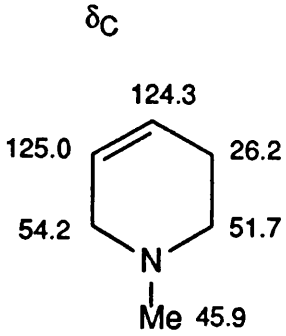












A.4 Tables of n.m.r. Spectral Data: 2-alkylpyridines.

^{1}H n.m.r. Spectral Data for 2-alkylpyridines (δ_H).									
Cpd.	6'	5'	4'	3'	1	2	3	4	Other.
(56)	8.49	7.16	7.63	7.18	2.93 3.03	4.59	5.95	5.11 5.31	5.20 (O*H*)
(57)	8.50	7.15	7.60	7.15	3.10	5.65	5.65	5.20	2.0 (Me)
(58)	8.46	7.12	7.59	7.24	3.05		5.87	4.90 5.14	7.10–7.30 (O*H*)
(62)	8.60	7.26	7.70	7.37	5.33		6.24	5.90 6.52	
(65)	8.60	7.40	7.40	7.40	3.30			2.30	1.2-1.5 (O*H*)
(70)	8.50	7.17	7.64	7.14	2.85 2.96		1.50	0.93	1.14 (Me) 5.5 (O*H*)
(68)	8.45	7.30	7.65	7.30	3.20	4.90		2.40	5.7 (O*H*)
(48)	8.56	7.18	7.64	7.23	7.06	6.73		3.15	
(50)	8.54	7.08	7.58	7.25	7.25	6.55	6.55	5.27 5.45	
(105)	8.67	7.28	7.75	7.50	2.40		7.17	7.54	
(109)	8.55	7.28	7.76	7.56	2.10		6.88		
(113)	8.68	7.32	7.76	7.48	4.35		7.43	7.70	

^{13}C n.m.r. Spectral Data for 2-alkylpyridines (δ_C).										
Cpd.	6'	5'	4'	3'	2'	1	2	3	4	Other.
(56)	148.5	121.5	136.7	123.7	159.5	43.2	71.9	140.1	114.6	
(58)	148.1	121.3	136.2	125.0	158.6	47.3	75.5	143.0	113.3	
(70)	148.3	121.3	136.7	124.4	160.0	46.4	72.8	34.7	8.5	26.3 (2-*Me*)
(62)	149.4	121.7	136.7	122.8	155.6	66.8	165.7	127.9	131.4	
(48)	149.7	122.3	136.6	123.2	153.6	141.8	111.4	82.5	81.1	
(113)	150.2	124.7	136.8	125.1	152.3	47.7	191.2	125.2	143.2	

A.5 Tables of n.m.r. Spectral Data: Isoxazoles/Isoxazolines.

^{1}H n.m.r. Spectral Data for isoxazoles (δ_H).								
Cpd.	6''	5''	4''	3''	2'	1'	4	Other.
(76)	8.65	7.25	7.72	7.40	7.63	7.42	6.65	7.48, 7.85 (Ph)
(45)	8.65	7.25	7.72	7.39	7.60	7.41	6.74	1.44 (*Me*)
								4.46 (CO_2CH_2Me)
(87)	8.65	7.38	7.87	7.67	7.67	7.54	7.07	4.69 (NH_2)
						7.57	7.15	10.11 ($CONHNH_2$)
(89)	8.64	7.23	7.70	7.35	7.50	7.33	6.86	7.22–7.24 (NH)
								1.54 [$C(Me)_3$]
(83)	8.56	7.16	7.60	7.13	3.32	3.20	6.40	1.41 (*Me*)
								4.42 (CO_2CH_2Me)

^{1}H n.m.r. Spectral Data for isoxazolines (δ_H).									
Cpd.	6''	5''	4''	3''	2'	1'	5	4	Other.
(49)	8.56	7.18	7.66	7.29	6.80	6.73	5.46	3.17	1.36 (*Me*)
								3.46	4.35 (CO_2CH_2Me)
(85)	8.53	7.16	7.62	7.20	2.90	2.15	4.85	2.91	1.36 (*Me*)
								3.28	4.34 (CO_2CH_2Me)

^{13}C n.m.r. Spectral Data for isoxazoles/isoxazolines (δ_C).											
Cpd.	6''	5''	4''	3''	2''	2'	1'	5	4	3	Other.
(45)	149.9	123.6	136.8	123.9	153.0	134.4	115.8	156.7	103.1	159.8	14.1 (*Me*) 62.1 ($CO_2C\,H_2Me$) 169.6 (*C*=O)
(87)	150.0	124.0	137.3	124.1	153.0	134.5	115.9	157.8	102.6	162.7	168.8 (*C*=O)
(89)	149.9	123.3	136.8	123.7	153.5	133.4	116.9	151.8	96.5	158.8	28.2 [$C(C\,H_3)_3$] 81.9 [$C\,(Me)_3$] 167.9 (*C*=O)
(83)	149.3	121.6	136.5	122.8	160.0	35.2	26.0	156.2	101.7	158.8	14.0 (*Me*) 61.9 ($CO_2C\,H_2Me$) 174.4 (*C*=O)
(49)	149.3	122.3	136.6	122.7	153.7	132.4	129.9	83.3	39.1	151.0	13.9 (*Me*) 61.9 ($CO_2C\,H_2Me$) 160.2 (*C*=O)
(85)	149.1	121.3	136.5	122.9	160.2	34.6	33.4	83.1	38.3	151.3	13.9 (Me) 61.8 ($CO_2C\,H_2Me$) 160.6 (*C*=O)

A.6 Tables of n.m.r. Spectral Data: Thiazoles.

^{1}H n.m.r. Spectral Data for thiazoles (δ_H).								
Cpd.	6"	5"	4"	3"	2'	1'	5	Other.
(41)	8.53	7.21	7.74	7.47	7.37	7.10	6.77	7.11 (NH_2)
(125)	8.54	7.10	7.57	7.13	3.10	2.95	6.04	5.50 (NH_2)
(129)	8.55	7.11	7.55	7.10	3.20	3.20	6.85	2.20 (pyrrole *Me*) 5.85 (pyrrole C*H*)
(131)	8.55	7.11	7.57	7.16	3.27	3.27	6.90	7.82 (γ-H) 7.98 (β-H)
(141)	8.49	7.20	7.69	7.20	2.97	2.78		7.20 (NH_2)

^{1}H n.m.r. Spectral Data for quaternary salts (δ_H).								
Cpd.	6"	5"	4"	3"	2'	1'	5	Other.
(114)	8.66	7.62	8.23	8.02	7.70	7.33	7.10	7.80–8.60 (NH_2)
(119)	8.93	7.86	8.45	8.45	7.71	7.25	7.19	4.28 (N^+Me) 7.30–7.50 (NH_2)
(132)	9.25	8.10	8.62	8.10	3.45	3.03	6.82	6.08 (CH_2Ph) 7.31–7.55 (γ,γ'-H, Ph) 7.85, 7.98 (β,β'-H)
(134)	9.03	7.99	8.51	8.08	3.55	3.32	7.55	4.35 (N^+Me) 7.99 (β,γ-H)

^{13}C n.m.r. Spectral Data for thiazoles (δ_C).											
Cpd.	6''	5''	4''	3''	2''	2'	1'	5	4	2	Other.
(41)	149.4	122.3	136.9	122.4	155.4	128.2	126.1	108.8	149.6	168.3	
(125)	149.2	121.0	136.2	122.8	161.1	37.3	31.5	102.5	152.0	167.7	
(131)	149.0	121.0	136.2	122.9	160.6	37.1	31.3	112.8	150.9	153.6	124.1 (β-C) 131.0 (α-C) 134.9 (γ-C) 164.6 (C=O)
(119)	144.1	124.5	145.9	124.6	148.1	135.5	116.7	115.6	152.5	168.6	45.7 (Me)
(134)	145.0	125.4	146.5	128.2	157.6	31.2	28.3	115.4	150.6	151.5	45.6 (Me) 124.0 (β-C) 131.0 (α-C) 135.4 (γ-C) 165.0 (C=O)

^{13}C N.m.r. Spectral Data for tetrahydropyridines (δ_C).											
Cpd.	6''	5''	4''	3''	2''	2'	1'	5	4	2	Other.
(120)	53.0	125.0	124.5	32.3	62.0	131.1	123.7	104.9	149.0	167.8	42.9 (N*Me*)
(123)	53.1	124.6	124.5	28.8	57.5	28.1	29.6	101.7	152.7	168.1	40.5 (N*Me*)
(124)	52.0	124.1	123.4	27.7	57.0	27.5	29.3	107.3	150.3	158.8	22.8 (CO*Me*) 39.3 (N*Me*) 168.3 (*C*=O)
(130)	47.9	125.0	124.3	28.5	55.2	27.6	28.7	102.2	153.3	167.3	56.2 (CH_2Ph) 126.7, 128.2, 128.8, 139.8 (Ph)
(135)	51.3	27.0	125.4	129.2	61.3	24.9	31.7	101.9	152.5	168.2	43.0 (N*Me*)

A.8 Table of u.v. Spectral Data.

U.v. Spectral Data.						
Cpd.	$\lambda_{max.}$ (nm). [ϵ ($dm^3\ mol^{-1}\ cm^{-1}$)].					
(45)		311 (24 670)	273sh (10 740)			209 (7 970)
(89)	325 (11 960)	311 (25 930)	269 (20 230)	264sh (19 610)	241 (15 830)	204 (43 050)
(76)	325 (14 200)	312 (33 380)	277sh (15 840)		244 (16 115)	200 (35 400)
(41)	329 (16 180)			257 (17440)		206 (8 830)
(114)	328 (20 830)			257 (23 900)		205 (19 470)
(119)	390 (6 560)		285sh (6 900)	268 (8 660)		207 (22 610)
(42)	315 (21 000)	300sh (18 000)		259 (18 000)	230sh (9 000)	
(161)		297 (8 640)		248 (7 540)		204 (12 470)
(90)		300 (16 400)			228 (29 000)	